

Aromatase inhibitor use, co-morbidities, and cardiovascular disease risk  
in breast cancer survivors

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**Abstract**

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Breast cancer survivors are a growing population with significant comorbidity burden. Approximately 80 percent of breast cancer cases are hormone receptor-positive and can be treated by endocrine therapy. Aromatase inhibitors (AIs) and tamoxifen are the two major types of endocrine therapies. Although AIs have more favorable breast cancer clinical outcomes than tamoxifen, AI-related cardiovascular disease (CVD) risk is a growing concern. Previous observational studies investigating the association between AI use and CVD risk have inconsistent results and may be biased for a few reasons, including not accounting for important confounders, not adequately accounting for immortal time bias, and misclassification of endocrine therapy use. Despite breast cancer guidelines and results from clinical trials emphasizing the importance of using AIs for more than 5 years, few studies have examined the duration of AI exposure when investigating AI-related CVD risk. In addition, no prior studies have examined the association between AI use and CVD risk in subgroups defined by breast cancer comorbidities, such as obesity, depression, and history of CVD prior to breast cancer diagnosis. Therefore, we leveraged data from the Pathways Heart Study and Pathways Study and conducted three studies to address the gaps in the literature.

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In Chapter 1, we examined the associations of endocrine therapy use with CVD and mortality risk in postmenopausal women with early-stage hormone receptor-positive breast cancer and whether the associations varied in strata defined by obesity, depression, and history of CVD prior to breast cancer diagnosis. We found that, compared with non-user of endocrine therapy, women who used AIs within 12 months after breast cancer diagnosis were less likely to develop major adverse cardiovascular events (hazard ratio [HR]= 0.85, 95% confidence interval [CI] =0.73 to 0.98) and heart failure (HR = 0.79, 95% CI = 0.65 to 0.97). No associations between tamoxifen use within 12 months and CVD outcomes were observed. Both AI and tamoxifen use within 12 months after breast cancer diagnosis were associated with lower risk of all-cause mortality and non-CVD-related mortality, and AI users were at approximately 30% lower risk of CVD-related mortality, compared with non-users of endocrine therapy. Tamoxifen users with normal body mass index (BMI) were at decreased risk of all-cause mortality (HR = 0.66, 95% CI = 0.51 to 0.87) and non-CVD-related mortality (HR = 0.57, 95% CI = 0.42 to 0.79) compared with non-users of endocrine therapy with normal BMI, whereas no associations of tamoxifen use with all-cause mortality and non-CVD-related mortality were observed in the overweight/obese subgroup ( $P$  for interaction <0.05). Our findings suggest that endocrine therapy reduces all-cause mortality risk and may not increase CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer.

In Chapter 2, we examined the associations of duration of AI use with CVD and mortality risk in postmenopausal women with early-stage hormone receptor-positive breast cancer and whether the associations varied in strata defined by obesity, depression, and history of CVD prior to breast cancer diagnosis. We observed a lower risk of stroke in intermediate-term AI users (HR = 0.60, 95% CI = 0.37 to 0.96) and long-term AI users (HR = 0.51, 95% CI = 0.30 to 0.85), than in short-term AI users. The longer duration of AI use was also associated with lower risk of all-cause mortality and non-CVD-related mortality. In addition, long-term AI users were at 37% lower risk of CVD-related mortality (HR = 0.63, 95% CI = 0.42 to 0.95) than short-term AI users. No significant differences were observed in risks of

major adverse cardiovascular events, ischemic heart disease, and heart failure across the three groups. The association between long-term AI use and non-CVD-related mortality differed in women with versus without a history of CVD prior to breast cancer diagnosis ( $P$  for interaction = 0.01); long-term AI users without CVD history were at lower risk of non-CVD-related mortality (HR = 0.47, 95% CI = 0.37 to 0.60) than short-term AI users without CVD history, whereas no such association was observed in the subgroup with CVD history. Our findings suggest that long-term AI use reduces all-cause mortality risk and may not increase CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer.

In Chapter 1 and 2, we examined the association between endocrine therapy use and CVD risk stratified by depression defined by the CES-D scale. However, only a small portion of participants completed the CES-D questionnaire, and thus our stratified analyses were underpowered. If the CES-D scale shows good agreement with ICD codes for depression, which are available for all study participants, we can use ICD codes to define depression and the stratified analysis by depression would have better power in Chapter 1 and 2. Hence, In Chapter 3, we leveraged data from the Pathways Study and examined the agreement between the self-reported Center for Epidemiologic Studies Depression (CES-D) scale for depressive symptoms and International Classification of Diseases (ICD)-9 diagnosis codes for depression in breast cancer survivors. We found that a total of 1,015 (25.7%) women had a CES-D score of 16 or more and were classified as depressed, while a total of 660 (16.7%) women were classified as depressed using ICD-9 codes. Depressive symptoms defined by the CES-D scale and depression defined by ICD-9 codes had slight agreement ( $\kappa = 0.16$ ). Their classification was significantly different ( $P < 0.0001$ ). Using the CES-D scale as the reference standard, the sensitivity and specificity of ICD-9 codes for depression were 42.3% and 77.6%, respectively. Our findings suggest that ICD-9 codes are not a valid measure of depression in epidemiology studies of breast cancer.

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## **Chapter 1: Endocrine therapy use and risk of cardiovascular disease and mortality in postmenopausal breast cancer survivors**

### **Abstract**

**Purpose:** Cardiovascular disease (CVD) has been an increasing concern in older breast cancer survivors, yet the association between breast cancer treatment including endocrine therapy and cardiovascular outcomes is controversial. Therefore, this study examined the risk of CVD and mortality associated with endocrine therapy use in postmenopausal women with early-stage hormone receptor-positive breast cancer.

**Methods:** A total of 8,495 postmenopausal women were included who were diagnosed with stage I-III hormone receptor-positive breast cancer from 2005 to 2013 and part of the Pathways Heart Study, a prospective cohort study in Kaiser Permanente Northern California (KPNC). Cancer treatment, CVD outcomes, mortality, and covariate data were obtained from KPNC electronic health records, pharmacy claims, and linkage to the KPNC mortality file. The landmark method, a statistical method used to mitigate immortal time bias, was used to calculate follow-up time, with 12 months after breast cancer diagnosis selected as the landmark time. Cause-specific hazards models were used to account for competing risks and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of endocrine therapy use [aromatase inhibitor use (AIs), tamoxifen use, or no use] with CVD and mortality outcomes. CVD outcomes included ischemic heart disease, heart failure, stroke, and major adverse cardiovascular events (MACE). Mortality outcomes included all-cause mortality, CVD-related mortality, and non-CVD-related mortality. Likelihood ratio tests were performed to examine whether the association of endocrine therapy use with CVD and mortality outcomes varied in strata defined by obesity, depression, and history of CVD prior to breast cancer diagnosis.

Results: Over a median follow-up of 7.5 years (interquartile range = 3.3 to 9.8), women who used AIs within 12 months after breast cancer diagnosis were less likely to develop MACE outcomes (HR= 0.85, 95% CI =0.73 to 0.98) and heart failure (HR = 0.79, 95% CI = 0.65 to 0.97) compared with non-users of endocrine therapy. No associations between tamoxifen use within 12 months and CVD outcomes were observed. Both AI and tamoxifen use within 12 months after breast cancer diagnosis were associated with lower risk of all-cause mortality (AI use: HR = 0.74, 95% CI = 0.67 to 0.82; tamoxifen use: HR = 0.82, 95% CI = 0.79 to 0.96) and non-CVD-related mortality (AI use: HR = 0.74, 95% CI = 0.66 to 0.84; tamoxifen use: HR = 0.77, 95% CI = 0.64 to 0.93), and AI users were at approximately 30% lower risk of CVD-related mortality (HR = 0.73, 95% CI = 0.59 to 0.91), compared with non-users of endocrine therapy. Tamoxifen users with normal body mass index were at decreased risk of all-cause mortality (HR = 0.66, 95% CI = 0.51 to 0.87) and non-CVD-related mortality (HR = 0.57, 95% CI = 0.42 to 0.79) compared with non-users of endocrine therapy with normal BMI, whereas no associations of tamoxifen use with all-cause mortality and non-CVD-related mortality were observed in the overweight/obese subgroup ( $P$  for interaction <0.05).

Conclusion: Compared with non-use of endocrine therapy within 12 months after breast cancer diagnosis, AI use was associated with lower risk of MACE, heart failure, all-cause mortality, CVD-related mortality, and non-CVD-related mortality outcomes in postmenopausal women with early-stage hormone receptor-positive breast cancer. Our findings suggest endocrine therapy use reduces all-cause mortality risk and may not increase CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer.

## Introduction

Breast cancer survivors are a growing population with significant comorbidity burden.<sup>1</sup> It is estimated that over 4 million women with a history of breast cancer live in the United States, and approximately 310,720 new cases are expected in 2024.<sup>2</sup> Although improvements in breast cancer detection and treatment have reduced breast cancer-specific mortality, death rates from other causes have been increasing in breast cancer survivors.<sup>3</sup> For breast cancer survivors aged 50 years and older, approximately 35% of non-breast cancer mortality is due to cardiovascular disease (CVD), making CVD the second most common cause of death after breast cancer in these patients.<sup>4</sup> In addition, we and others have reported on elevated CVD risk in breast cancer survivors compared with women without breast cancer.<sup>5-8</sup> Given the excess CVD risk in breast cancer survivors, identifying CVD causal risk factors is imperative in this population to develop effective mitigation strategies.

Aromatase inhibitors (AIs) and selective estrogen receptor modulators are the two major types of endocrine therapies used to treat hormone receptor-positive breast cancer. AIs lower estrogen levels by stopping its production in fat tissues. As AIs do not affect ovarian estrogen production, AIs are prescribed for postmenopausal women.<sup>9,10</sup> Unlike AIs, tamoxifen is a selective estrogen receptor modulator and does not stop the production of estrogen. Instead, tamoxifen blocks estrogen from binding to breast cancer cells and is prescribed for premenopausal women.<sup>8</sup> Tamoxifen is a selective estrogen receptor modulator and has estrogen agonistic activity in the cardiovascular system. Specifically, it may increase levels of potentially cardioprotective endogenous estrogens.<sup>11</sup> Increased endogenous estrogen levels may decrease atherosclerosis, risk of hypertension, and inflammation due to its impact on vascular endothelial cells, vascular smooth muscle cells, and cardiomyocytes, lipid profiles, and oxidative stress.<sup>11-16</sup> Tamoxifen can also be used as an alternative treatment for postmenopausal women who suffer from AI side effects, such as hot flashes, muscle and joint pain, and osteoporosis.<sup>9,10,17</sup>

Although AIs have been associated with better breast cancer clinical outcomes compared with tamoxifen,<sup>18</sup> including decreased risks of all-cause and breast cancer-specific mortality, AI-related CVD risk compared with tamoxifen is a growing concern. We previously reported that breast cancer survivors who used AIs were at higher CVD risk than women without a history of breast cancer.<sup>8</sup> However, there is mixed evidence on the CVD risk of endocrine therapy use when the reference group is breast cancer survivors who used tamoxifen. Over the last decade, several systematic reviews have examined CVD risk for AIs compared with tamoxifen in breast cancer patients;<sup>19-23</sup> three of the five systematic reviews report elevated CVD risk in AI users compared with tamoxifen users,<sup>20,21,23</sup> while the other two systematic reviews suggest no association between AI use and CVD risk.<sup>19,22</sup> The observed higher CVD risk in AI users compared with tamoxifen users may be partly driven by cardioprotective effects of tamoxifen.<sup>10,11</sup> A few recent observational studies have investigated the association between AI use and CVD risk.<sup>24-31</sup> Similar to the results of systematic reviews, the conclusions from these observational studies are inconsistent. The results of these observational studies may be biased for a few reasons, including (1) not accounting for important confounders, such as smoking, body mass index (BMI) and clinical predictors of incident CVD, (2) not adequately accounting for immortal time bias, and (3) misclassification of endocrine therapy use.

When considering AI-related CVD risk in breast cancer survivors, it is also important to examine potential effect modifiers of AI-related CVD risk to identify subgroups of women that may be particularly vulnerable to the potential harm of AIs on cardiovascular health. Therefore, important comorbidities should be considered. Excess adiposity may lead to alterations in drug pharmacokinetics and pharmacodynamics.<sup>32,33</sup> suggesting a potential interaction between endocrine therapy use and obesity. Depression is linked with both CVD risk and lower medication adherence,<sup>34-36</sup> suggesting a potential interaction of endocrine therapy use with depression. One trial reported that in women with preexisting heart disease, CVD events were higher in the AI arm than the tamoxifen arm.<sup>37</sup> Thus, a need exists to

examine whether the association between endocrine therapy use and CVD risk is different in subgroups of breast cancer patients with different comorbidities (i.e., obesity, depression, and CVD history).

Given the increasing concerns of cardiovascular safety of endocrine therapy use, we conducted a prospective cohort study to examine the associations of endocrine therapy use with CVD risk and mortality in postmenopausal women with early-stage hormone receptor-positive breast cancer. To identify potential subgroups of breast cancer survivors at high risk of CVD and mortality, we examined whether breast cancer comorbidities, including obesity, depression, and CVD history, modified potential associations of endocrine therapy use with CVD risk and mortality. We hypothesized that AI use would elevate CVD risk whereas tamoxifen use would reduce CVD risk when compared with non-users of endocrine therapy. Additionally, due to the established reduction in breast cancer mortality associated with AI and tamoxifen use,<sup>38,39</sup> we hypothesized AI and tamoxifen use would reduce all-cause and non-CVD-related mortality risk, compared with non-users of endocrine therapy.

## **Methods**

### *Study population*

The National Cancer Institute (NCI)-funded Pathways Heart Study (R01CA214057, MPIs: Kwan and Greenlee) is an ongoing, prospective cohort study within Kaiser Permanente Northern California (KPNC). Its aim is to examine incident CVD and cardiometabolic risk factors in women with breast cancer. The KPNC electronic health record (EHR) was utilized to identify eligible women and to extract their administrative and clinical data. Inclusion criteria for the Pathways Heart Study included diagnosis of stage I-IV breast cancer from November 2005 to March 2013, no previous history of invasive cancer, female, 21 years or older, and continuous KPNC membership for at least 12 months before the breast cancer diagnosis date, allowing for up to a 31-day gap in membership. For this analysis, the inclusion criteria were: (1) postmenopausal women with a first-ever diagnosis of stage I-III breast cancer from November 2005 to March 2013; and (2) patients eligible for endocrine therapy, (i.e., diagnosed with

estrogen or progesterone receptor-positive breast cancer). Exclusion criteria were: (1) women with evidence of metastatic disease because advanced disease stage may lead to significant variability in treatment response and prognosis, potentially confounding the study results ( $n = 320$ );<sup>40,41</sup> (2) women with AI and/or tamoxifen prescriptions prior to their breast cancer diagnosis because the study focused on breast cancer treatment rather than prevention ( $n = 17$ ); and (3) women who switched to AI from tamoxifen or vice versa within 12 months after breast cancer diagnosis to avoid exposure misclassification ( $n = 322$ ). Figure 1 presents the consort diagram.

#### *Data collection and measures*

Covariate data abstracted from the EHR included age, race, socioeconomic characteristics (i.e., percent neighborhood education of college graduate or higher and neighborhood median household income), BMI, waist circumference, smoking history, the Comorbidity Point Score Version 2 (COPS2), and the Center for Epidemiologic Studies Depression (CES-D) score at baseline, which was defined as the date of breast cancer diagnosis. COPS2 is a measure of comorbidity developed and used internally at KPNC.<sup>42</sup> It is calculated using diagnostic codes of inpatient and outpatient encounters occurring in the year before diagnosis.<sup>42</sup> The CES-D scale was developed for epidemiology studies of depression and was administered to women enrolled in the main Pathways Study.<sup>43,44</sup> A CES-D score of 16 points or more was considered as having depression.<sup>43</sup> Overweight or obese was defined as a BMI greater than or equal to  $25.0 \text{ kg/m}^2$ , and central obesity was defined as a waist circumference greater than or equal to the median value (95.2 cm) for the population. Data on waist circumference were only available in women who enrolled in the main Pathways Study.<sup>44</sup> Using clinically meaningful cutoff point of waist circumference would yield a very small sample size in the normal waist circumference group, and thus we used the median value of waist circumference to define central obesity. Baseline diabetes was identified as entry into the KPNC Diabetes Registry prior to the breast cancer diagnosis.<sup>45</sup> Inclusion criteria of entering into the KPNC Diabetes Registry are any one of the following: (1) at least one principal inpatient diagnosis of International Classification of Diseases 9th revision, clinical modification (ICD-9-CM) 250.xx or

equivalent ICD-10-CM codes; (2) at least two outpatient diagnoses spanning the current and previous 5 years; (3) two or more abnormal laboratory test results on separate days spanning the current year and the past 2 years (i.e., fasting blood glucose  $\geq$  126 mg/dL); and (4) at least one diabetes medication prescription such as insulin, oral hypoglycemics, or insulin sensitizers.<sup>45</sup> Patients with only one of the indicators must have additional indicators during the subsequent 2 years of KPNC membership.<sup>45</sup>

Baseline dyslipidemia was defined any of the following within 3 years prior to breast cancer diagnosis (1) two separate ICD diagnosis codes (ICD-9-CM 272.0-272.4, ICD-10 E78.00, E78.01, and E78.1-R78.5); (2) a diagnosis code and abnormal laboratory results (low-density lipoprotein cholesterol  $\geq$  160 mg/dL); (3) a diagnosis code and lipid-lowering medication use; or (4) lipid-lowering medication use and abnormal laboratory test results.<sup>45</sup> Baseline hypertension was defined as any of the following within 3 years prior to breast cancer diagnosis: (1) two separate ICD diagnosis codes (ICD-9-CM 401.xx or equivalent ICD-10-CM codes) at primary care visits; (2) one diagnosis code at primary care visit and one hospitalizations with a primary or secondary hypertension diagnosis; or (3) one diagnosis code at primary care visit and one filled prescription for hypertension medication.<sup>45</sup> Baseline CVD history was defined using ICD diagnostic codes and Current Procedural Terminology codes from inpatient, ambulatory, and emergency department encounters and/or hospital discharge records within 3 years prior to the breast cancer diagnosis (Supplemental Table 1).

#### *Classification and verification of non-users of endocrine therapy*

Data on cancer characteristics and receipt of chemotherapy, radiation therapy, and endocrine therapy were obtained from the KPNC Cancer Registry and supplemented by procedure, infusion, and outpatient pharmacy data sources. One pharmacy fill of an endocrine therapy drug within 12 months after breast cancer diagnosis was used to infer endocrine therapy use.<sup>25</sup> Study participants were classified into one of three endocrine therapy categories: (1) non-users; (2) AI users only; or (3) tamoxifen users only. Women who switched between AIs and tamoxifen within 12 months after breast cancer diagnosis were excluded to avoid misclassification (additional details are described in the Statistical Analysis section).

We identified 1,210 women who had a diagnosis of hormonal receptor-positive breast cancer but who did not have a pharmacy claim indicating use of endocrine therapy. The characteristics of the 1,210 women at breast cancer diagnosis are presented in Supplemental Table 2. To verify whether these women without pharmacy claims were true non-users of endocrine therapy, clinician notes from the EHR within the 2 years after breast cancer diagnosis for these women were reviewed. Given the significant number of notes, we only reviewed notes related to endocrine therapy, (i.e., notes containing the following key words: endocrine therapy, hormone therapy, aromatase inhibitor, AI, AIs, tamoxifen, TAM, SERM, selective estrogen receptor modulator, SERD, selective estrogen receptor degrader, hormonal TX, hormonal treatment, hormonal therapy, hormone TX, hormone treatment, anastrozole, Arimidex, exemestane, Aromasin, letrozole, Femara, Nolvadex, and Soltamox). We identified 9,781 notes for 1,080 women and the author Y.H. reviewed all of the notes. There were 130 (10.7%) women who did not have related notes within the 2 years after breast cancer diagnosis. Women (n=121 (10.0%)) were coded as endocrine therapy users if the notes indicated that a woman had agreed to or initiated endocrine therapy, and these users were excluded from this study. Women (n=847 (70.0%)) were coded as true non-users if the notes indicated that a woman declined endocrine therapy. Some women (n=112 (9.3%)) did not have EHR notes that indicated whether they agreed to or declined endocrine therapy, and these women were classified as not having enough information. The 130 (10.7%) women without related notes and the 112 (9.3%) women without enough information were coded as non-users in the main analysis.

#### *Outcome ascertainment*

Cardiovascular events through December 31, 2021 were identified from the KPNC EHR according to the ICD diagnostic codes and Current Procedural Terminology codes from inpatient, ambulatory, and emergency department encounters and/or hospital discharge records (Supplemental Table 1). Data on death date and cause of death through December 31, 2021, were obtained from linkage to the KPNC mortality file, which is regularly updated with data from the California State Department of Vital

Statistics, US Social Security Administration, National Death Index, and KPNC membership. The primary CVD outcome was a composite of major adverse cardiovascular events (MACE), including ischemic heart disease (IHD), heart failure (HF), stroke, and CVD-related death. CVD-related death was defined as death due to IHD, stroke, HF, cardiomyopathy, arrhythmia, cardiac arrest, myocarditis/pericarditis, valvular disease, venous thromboembolism, and carotid disease. Secondary CVD outcomes were IHD, HF, and stroke. Fatal CVD events were included in the corresponding CVD outcomes. Mortality outcomes included all-cause mortality, CVD-related mortality, and non-CVD-related mortality.

### *Statistical analysis*

Baseline characteristics of study participants were summarized using the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Follow-up time was calculated using the landmark method to mitigate immortal time bias.<sup>46</sup> The landmark method refers to the analysis designating a time point occurring during the follow-up period (known as the landmark time) and analyzing only those subjects who have not developed outcome events by the landmark time. This study used 12 months after breast cancer diagnosis as the landmark time because over 90% of users initiated endocrine therapy within 12 months after breast cancer diagnosis. Women who switched endocrine therapy drugs or developed outcome events before the landmark time were excluded. The characteristics of women who were excluded due to the landmark method are presented in Supplemental Table 3. The follow up commenced 12 months after breast cancer diagnosis and ended on the date the outcome event occurred, health plan disenrollment, death, or end of study (December 31, 2021), whichever occurred first. Cause-specific hazards models were used to account for competing risks and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the association of AI use with mortality and CVD outcomes. Complete cases analyses were performed. These models were adjusted for potential confounders including age at breast cancer diagnosis, race, percent neighborhood education of college graduate or higher, neighborhood median household income, BMI, history of ever smoking,

American Joint Committee on Cancer (AJCC) stage, chemotherapy, and radiation, and additionally adjusted for precision covariates including diabetes, dyslipidemia, hypertension, and COPS2. Potential effect modification of general and central obesity, depression, and CVD history was examined using likelihood ratio tests. The effect modification analyses were only performed within subgroups which had at least 10 outcome events per exposure group to obtain more accurate estimation of the regression coefficients.<sup>47</sup> All analyses were performed using R (version 4.3.2, R development Core Team (2023)).<sup>48</sup>

### *Sensitivity analyses*

Sensitivity analyses were conducted to examine four potential issues, including confounding by indication, immortal time bias, an additional landmark time, misclassification of non-users of endocrine therapy, and consistency assumption. The first sensitivity analysis compared AI use and non-use of endocrine therapy with tamoxifen use to avoid confounding by indication. Confounding by indication occurs when clinical indication for treatment also affects the outcome of interest. Our main analysis compared users of endocrine therapy with non-users of endocrine therapy, and there might be an underlying clinical indication for endocrine therapy which also affects CVD risk. Therefore, confounding by indication is a concern of our main analysis. The second sensitivity analysis used a naïve method to calculate follow-up time. The naïve method followed non-users of endocrine therapy from the breast cancer diagnosis date, while it followed users from the first dispensing date of AIs or tamoxifen. Unlike the landmark method, which defined endocrine therapy use within the 12 months after breast cancer diagnosis, the naïve method defined endocrine therapy users as having one pharmacy fill of an endocrine therapy any time during follow-up. This sensitivity analysis provided evidence on the magnitude of immortal time bias caused by the naïve method. The third sensitivity analysis used six months after breast cancer diagnosis as the landmark time. The landmark method may adopt several landmarks as the selection of landmarks should consider clinical relevance and study power. Thus, we selected six months after breast cancer diagnosis as an additional landmark to increase study power. The fourth sensitivity analysis excluded the 242 participants with unknown status of endocrine therapy use. This sensitivity

analysis only included verified non-users of endocrine therapy and avoided bias by measurement error. The last sensitivity analysis excluded participants with a medication possession ratio less than 80%. The medication possession ratio was estimated as the number of days supplied (excluding last refill) divided by the number of days between the first and last dispense dates. Including endocrine therapy users with low adherence may violate the consistency assumption and introduce bias. Thus, this sensitivity analysis excluded endocrine therapy users with low adherence.

## **Results**

### *Baseline characteristics*

A total of 8,495 postmenopausal women diagnosed with hormone receptor-positive breast cancer from 2005-2013 were included in this study. The average age of study participants was 66.6 years old (standard deviation = 9.7) and 71% were white (Table 1). In AI users, 94.2% used anastrozole, 8.8% used letrozole, and 3.1% used exemestane. Compared with non-users of endocrine therapy, AI users were more likely to be younger, live in neighborhoods with higher levels of median household income, have an obese BMI, have higher waist circumference, be diagnosed at a later breast cancer stage, receive chemotherapy, receive radiation, have a lower COPS2 (i.e., fewer comorbidities), and were less likely to have prevalent CVD at baseline. Compared with non-user of endocrine therapy, tamoxifen users were more likely to be younger, be diagnosed at a later breast cancer stage, receive chemotherapy, receive radiation, have a lower COPS2 (i.e., fewer comorbidities), and were less likely to have prevalent CVD, diabetes, dyslipidemia, and hypertension at baseline.

### *CVD risk and mortality risk*

Table 2 presents the results of the main association analysis. Over a median follow-up of 7.5 (interquartile range = 3.3 to 9.8) years, women who used AIs within 12 months after breast cancer diagnosis were less likely to develop MACE (HR = 0.84, 95% CI = 0.73 to 0.97) and HF (HR = 0.79, 95% CI = 0.65 to 0.97), than non-users of endocrine therapy. No differences in risks of IHD and stroke between AI users and non-

users of endocrine therapy were observed. Women who used tamoxifen within 12 months after breast cancer had similar risks of CVD outcomes including MACE, IHD, stroke, and HF compared with non-users of endocrine therapy.

Both AI users and tamoxifen users had lower risk of all-cause mortality and non-CVD-related mortality than non-users of endocrine therapy. In addition, AI users had approximately 30% lower risk of CVD-related mortality (HR = 0.73, 95% CI = 0.59 to 0.81), than non-users of endocrine therapy.

#### *Interaction analysis: Obesity*

Table 3 presents the results examining the interaction between endocrine therapy use and overall obesity, as defined by BMI. Evidence of an interaction was found between tamoxifen use and BMI category in relation to all-cause mortality and non-CVD-related mortality ( $P$  for interaction = 0.02 and 0.01, respectively); in women with normal BMI, tamoxifen users were at decreased risk of all-cause mortality (HR = 0.66, 95% CI = 0.51 to 0.87) and non-CVD-related mortality (HR = 0.57, 95% CI = 0.42 to 0.79), whereas no association between tamoxifen use and non-CVD-related mortality was observed in the overweight or obese subgroup. No interactions between AI use and overall obesity on risk of CVD and mortality outcomes were observed.

Table 4 presents the results examining the interaction between endocrine therapy use and central obesity, as defined by waist circumference. No interactions between AI use or tamoxifen use and waist circumference were observed.

#### *Interaction analysis: Depression*

Table 5 presents the results examining the interaction between endocrine therapy use and depression. No interactions between AI use or tamoxifen use and depression were observed.

### *Interaction analysis: History of prior CVD*

Table 6 presents the results examining the interaction between endocrine therapy use and history of CVD prior to breast cancer diagnosis. No interactions between AI use or tamoxifen use and prior history of CVD were observed.

### *Sensitivity analyses*

Supplemental Table 4 presents the results of sensitivity analysis comparing AI use and non-use of endocrine therapy with tamoxifen use. AI use within 12 months after breast cancer diagnosis was associated with lower risk of CVD-related mortality (HR = 0.76, 95% CI = 0.57 to 0.99) than tamoxifen use. Non-use of endocrine therapy within 12 months after breast cancer diagnosis was associated with higher risk of all-cause mortality (HR = 1.22, 95% CI = 1.05 to 1.44) and non-CVD-related mortality (HR = 1.30, 95% CI = 1.08 to 1.56). We did not observe associations between AI use and the risk of MACE, IHD, stroke, HF, all-cause mortality, and non-CVD-related mortality.

Supplemental Table 5 presents the results of sensitivity analysis using the naïve method (non-users followed from date of breast cancer diagnosis and users followed from date of first dispensing of AI or TAM). With the existence of immortal time bias, the results of the naïve method suggested an inverse association between AI use and IHD risk (HR = 0.76, 95% CI = 0.60 to 0.96) and an inverse association between tamoxifen use and HF risk (HR = 0.69, 95% CI = 0.49 to 0.99), compared with non-users of endocrine therapy.

Supplemental Table 6 presents the results of sensitivity analysis using six months after breast cancer diagnosis as the landmark time. The results barely changed when changing the landmark time from 12 months to six months after breast cancer diagnosis.

Supplemental Table 7 presents the results of sensitivity analysis excluding the 242 women with an unknown status of endocrine therapy use. In this sensitivity analysis, AI use within 12 months after breast cancer diagnosis was no longer associated with a lower risk of MACE (HR = 0.88, 95% CI = 0.75 to 1.02), and other associations observed in the main analysis remained unchanged.

Supplemental Table 8 presents the results of sensitivity analysis excluding women with a medication possession ratio less than 80%. The results were consistent with those in the main analysis.

## **Discussion**

In this prospective cohort study of postmenopausal women with early-stage hormone receptor-positive breast cancer, AI use within 12 months after breast cancer diagnosis was associated with lower risks of MACE, HF, all-cause mortality, CVD-related mortality, and non-CVD-related mortality compared with non-use of endocrine therapy. Although tamoxifen use within 12 months after breast cancer diagnosis was not associated with CVD risk, it was associated with decreased risk of all-cause mortality and non-CVD-related mortality, possibly due to a reduction in breast cancer-specific mortality. The associations of tamoxifen use with all-cause mortality and non-CVD-related mortality were modified by BMI; tamoxifen users with normal BMI were at decreased risk of mortality compared with non-users with normal BMI, whereas no association was observed in the overweight/obese subgroup. The results of our study need to be interpreted along with the selected landmark time; our study can only indicate CVD and mortality risk comparing women who used AIs or tamoxifen with non-users of endocrine therapy within six or 12 months following breast cancer diagnosis. We hypothesized that AI use would elevate CVD risk by decreasing levels of potentially cardioprotective endogenous estrogen and tamoxifen would reduce CVD risk by acting like estrogen in cardiovascular system.<sup>11,15,16</sup> However, our findings are inconsistent with this hypothesis.

The biological mechanism of the observed inverse association between AI use and the risk of MACE and HF is unclear. One hypothesis is that AI users often take bisphosphonates to prevent bone fractures and using bisphosphonates may be cardioprotective. However, evidence of cardioprotective effect of bisphosphonates is mixed.<sup>49-51</sup> The observed inverse association might be due to different sources of bias. One of the sources is confounding by indication, which occurs when clinical indication for treatment also affects the outcome of interest. Although women who were ineligible for endocrine therapy were excluded, our study may still be subject to some degree of confounding by indication. For example, frail patients tend to have a lower likelihood of receiving medication treatment than healthier patients,<sup>52</sup> and thus non-users would appear to be more likely to develop adverse outcomes than users of medication. Other sources of bias include residual confounding by inadequate adjustment and confounding by unmeasured factors such as diet and physical activity, although the direction of the confounding is unpredictable. However, among all the possible explanations, one that should not be neglected is that our hypothesis is wrong and AI use does not elevate CVD risk.

We previously reported that breast cancer survivors who used AIs were at higher CVD risk than women without a history of breast cancer,<sup>8</sup> but the present study did not find elevated CVD risk associated with AI use. Our previous study may be subject to confounding by indication; breast cancer and CVD have some common risk factors and breast cancer survivors who received endocrine therapy are sicker than women without a history of breast cancer. Thus, AI use would appear to be harmful when comparing women with breast cancer to those without a history of breast cancer. Many prior studies have focused on a comparison between AIs and tamoxifen and observed elevated CVD risk with AI use.<sup>24,27,53-55</sup> However, the increased risk of CVD events observed in AI users is likely to be driven by a cardioprotective effect of tamoxifen.<sup>20,21</sup> As a selective estrogen receptor modulator, tamoxifen acts like estrogen, a protector of cardiovascular health, in the cardiovascular system.<sup>10,11</sup> Some studies have investigated CVD risk comparing AIs and tamoxifen to non-users of endocrine therapy.<sup>25,56</sup> Matthews et al. conducted a prospective cohort study in postmenopausal women with breast cancer using US Surveillance,

Epidemiology and End Results-Medicare data.<sup>25</sup> They followed up with study participants from one year after breast cancer diagnosis and defined endocrine therapy use as at least one fill of the endocrine therapy medication without specifying the time frame.<sup>25</sup> Therefore, their study may be subject to immortal time bias. They found that ever use of AIs was associated with a lower risk of HF (HR = 0.84, 95% CI = 0.75 to 0.94) compared with non-use of endocrine therapy, which is consistent with our study results.<sup>25</sup> They also found a reduced risk of stroke in AI ever users (HR = 0.87, 95% CI = 0.76 to 0.98) and tamoxifen ever users (HR = 0.82, 95% CI = 0.69 to 0.98) when compared with non-users.<sup>25</sup> However, our study did not observe that, which may be due to lack of study power and/or Matthew et al.'s study was confounded by immortal time bias. A recent population-based study conducted by Kim et al. reported that AI use in a subgroup of postmenopausal women with breast cancer was not associated with increased risk of coronary heart disease (HR = 0.91, 95% CI = 0.70 to 1.18), stroke (HR = 1.07, 95% CI = 0.81 to 1.42), or HF (HR = 1.11, 95% CI = 0.76 to 1.64), compared with non-users of endocrine therapy.<sup>56</sup> Consistent with our study, this study did not find associations of selective estrogen receptor modulators (tamoxifen and toremifene) with CVD outcomes (coronary heart disease: HR = 1.02, 95% CI = 0.75 to 1.37; stroke: HR = 0.82, 95% CI = 0.58 to 1.18; HF: HR = 1.40, 95% CI = 0.86 to 2.29) in the postmenopausal subgroup.<sup>56</sup> Kim et al.'s study accounted for immortal time bias using time-dependent Cox regression models.<sup>56</sup> The discrepant results between our study and Kim et al.'s study for HF risk comparing AI users with non-users may result from the differences in study population and definition of endocrine therapy use. Our study included postmenopausal women with hormone receptor-positive breast cancer while Kim et al. included postmenopausal women regardless of hormone receptor status. We defined endocrine therapy use and excluded participants who switched drugs at 12 months after breast cancer diagnosis and verified non-use of endocrine therapy from clinician EHR notes, while Kim et al. defined endocrine therapy use using prescription records after breast cancer diagnosis without specifying the timeframe and did not verify non-use of endocrine therapy. Inconsistencies between the two studies may be due to study power. For example, our study followed participants approximately 4 years longer than Kim's study, and thus had more time for CVD events to develop.

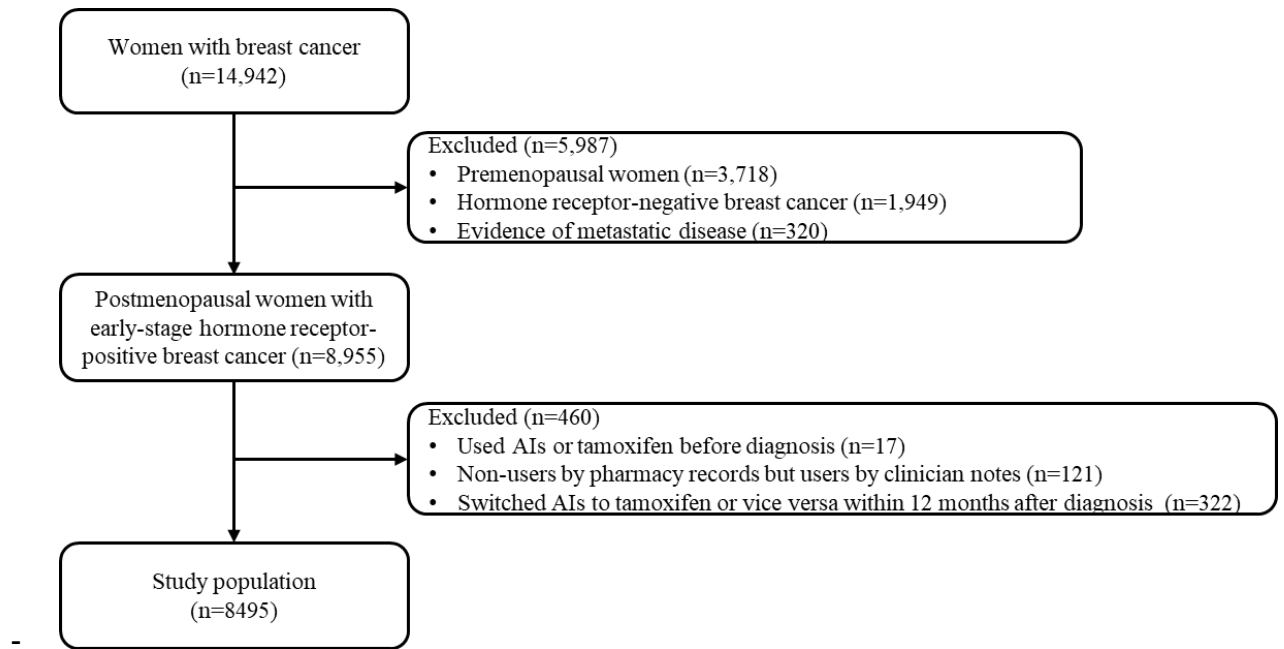
Compared with prior studies, our study has many strengths. First, instead of using pharmacy claims data only to infer non-use of endocrine therapy, we reviewed provider EHR notes to verify whether women without pharmacy data on endocrine therapy use were true non-users and thus increased the validity of the measure. Second, our study accounted for immortal time bias using the landmark method. Immortal time bias arises when, during the period of observation, time intervals are present during which the outcome events cannot occur (i.e., immortal time).<sup>57</sup> To be specific, the time interval between breast cancer diagnosis and initiation of endocrine therapy is “immortal” for users of endocrine therapy. Therefore, we used the landmark method to ensure that all time intervals during which study participants may experience the outcome of interest are captured and included in the analysis. We also performed sensitivity analyses to examine the magnitude of immortal time bias and found substantial immortal time bias. In addition, our measurement of endocrine therapy use considered both drug switching and adherence; women who switched the drug were excluded and we performed sensitivity analyses excluding patients with low medication possession ratio. Moreover, we examined the effect modification by comorbidities including obesity, depression, and history of CVD prior to breast cancer diagnosis and found the interaction between tamoxifen use and BMI on the risk of all-cause mortality and non-CVD-related mortality.

Our study has several limitations. First, misclassification of exposure is possible. Endocrine therapy use was measured by pharmacy prescription records. Nevertheless, filling a pharmacy prescription does not always indicate that the drug was taken by the patient. Furthermore, this study did not take duration of endocrine therapy use into account, which is an important therapeutic characteristic of the treatment. We also did not consider type of AI type. Anastrozole, letrozole and exemestane are third-generation AIs currently in clinical use. None of the three AIs is superior to the others in terms of efficacy as adjuvant treatments for hormone receptor-positive breast cancer,<sup>58</sup> and results from RCTs found that the three AIs have similar effects on CVD risk.<sup>58-62</sup> In our cohort, over 90% of AI users used anastrozole. Therefore, we

did not examine CVD risk by individual AI agent. Further, women in our study were diagnosed with breast cancer from 2005 to 2013 and their utilization patterns of endocrine therapy may be different from what it is being used now. Moreover, this study may be subject to confounding by indication due to comparing users to non-users of endocrine therapy. To reduce this confounding by indication, we only included patients who were eligible for endocrine therapy, (i.e., having hormone receptor-positive breast cancer, and reviewed their clinicians' notes to confirm they were true non-users). We also performed sensitivity analysis comparing AI users to tamoxifen users to avoid confounding by indication. In addition, data on CES-D score and waist circumference were only available in women who enrolled in the main Pathways Study,<sup>44</sup> and thus the precision of HRs is limited in strata defined by CES-D score and waist circumference. Another consideration is that the generalizability of results to populations outside of the KPNC population may be limited as women in the study have higher household median incomes and education levels compared with the general U.S. population. Yet, KPNC provides care to over 30% of the underlying population in counties where they are physically located, and aside from having health insurance, is generally representative of the catchment area. Furthermore, although the study adjusted for multiple confounders, confounding and bias cannot be completely ruled out due to the observational nature of this study.

In conclusion, in postmenopausal women with early-stage hormone receptor-positive breast cancer, we found evidence that AI use at 12 months after breast cancer diagnosis was associated with lower risks of MACE, HF, all-cause mortality, CVD-specific mortality, and non-CVD-related mortality, compared with non-users of endocrine therapy. Tamoxifen use within 12 months after breast cancer diagnosis was associated with lower risk of all-cause mortality and non-CVD-related mortality when compared with non-users of endocrine therapy, and the associations of tamoxifen use with all-cause mortality and non-CVD-related mortality were modified by BMI. No evidence was found of elevated CVD risk associated with AI or tamoxifen use within 12 months or later after breast cancer diagnosis, suggesting endocrine therapy use reduces all-cause mortality risk and may not increase CVD risk in postmenopausal patients

with early-stage hormone receptor-positive breast cancer. Although our findings are observational and not definitive, these findings can help inform future hypotheses to test. Future studies should account for treatment duration to examine the potential dose-response relationship between AI use and CVD risk.



**Figure 1. Consort diagram of study population**

**Table 1. Characteristics of study participants at breast cancer diagnosis by endocrine therapy type (n=8,495)**

|                                                                                | <b>Non-user<br/>(n=1,439)</b> | <b>AI<br/>(n=6,131)</b> | <b>Tamoxifen<br/>(n=925)</b> | <b>Overall<br/>(n=8,495)</b> |
|--------------------------------------------------------------------------------|-------------------------------|-------------------------|------------------------------|------------------------------|
| <b>Age at diagnosis, y, mean (SD)</b>                                          | 70.4 (11.1)                   | 66.1 (8.8)              | 64.4 (11.1)                  | 66.6 (9.7)                   |
| <b>Race/ethnicity, n (%)</b>                                                   |                               |                         |                              |                              |
| American Indian and Alaska Native                                              | 16 (1.1%)                     | 35 (0.6%)               | 8 (0.9%)                     | 59 (0.7%)                    |
| Asian                                                                          | 152 (10.6%)                   | 777 (12.7%)             | 111 (12.0%)                  | 1,040 (12.2%)                |
| Black                                                                          | 102 (7.1%)                    | 333 (5.4%)              | 54 (5.8%)                    | 489 (5.8%)                   |
| Hispanic                                                                       | 145 (10.1%)                   | 619 (10.1%)             | 94 (10.2%)                   | 858 (10.1%)                  |
| Pacific Islander                                                               | 3 (0.2%)                      | 24 (0.4%)               | 1 (0.1%)                     | 28 (0.3%)                    |
| White                                                                          | 1,021 (71.0%)                 | 4,343 (70.8%)           | 657 (71.0%)                  | 6,021 (70.9%)                |
| <b>Percent neighborhood education of college graduate or higher, Mean (SD)</b> |                               |                         |                              |                              |
| Mean (SD)                                                                      | 0.228 (0.115)                 | 0.237 (0.114)           | 0.227 (0.109)                | 0.234 (0.114)                |
| Missing                                                                        | 45 (3.1%)                     | 61 (1.0%)               | 22 (2.4%)                    | 128 (1.5%)                   |
| <b>Neighborhood median household income, \$, Mean (SD)</b>                     |                               |                         |                              |                              |
| Mean (SD)                                                                      | 77,100 (32,900)               | 82,000 (34,500)         | 79,600 (35,000)              | 80,900 (34,400)              |
| Missing                                                                        | 45 (3.1%)                     | 61 (1.0%)               | 22 (2.4%)                    | 128 (1.5%)                   |
| <b>BMI category</b>                                                            |                               |                         |                              |                              |
| Underweight                                                                    | 43 (3.0%)                     | 46 (0.8%)               | 21 (2.3%)                    | 110 (1.3%)                   |
| Normal                                                                         | 481 (33.4%)                   | 1,674 (27.3%)           | 328 (35.5%)                  | 2,483 (29.2%)                |
| Overweight                                                                     | 463 (32.2%)                   | 2,004 (32.7%)           | 302 (32.6%)                  | 2,769 (32.6%)                |
| Obese                                                                          | 447 (31.1%)                   | 2,406 (39.2%)           | 274 (29.6%)                  | 3,127 (36.8%)                |
| Missing                                                                        | 5 (0.3%)                      | 1 (0.0%)                | 0 (0%)                       | 6 (0.1%)                     |
| <b>BMI, kg/m<sup>2</sup></b>                                                   |                               |                         |                              |                              |
| Mean (SD)                                                                      | 28.0 (6.56)                   | 29.2 (6.40)             | 27.5 (5.96)                  | 28.8 (6.41)                  |
| Missing                                                                        | 5 (0.3%)                      | 1 (0.0%)                | 0 (0%)                       | 6 (0.1%)                     |
| <b>Waist circumference, cm</b>                                                 |                               |                         |                              |                              |
| Mean (SD)                                                                      | 94.1 (16.2)                   | 97.4 (16.4)             | 92.6 (14.5)                  | 96.4 (16.3)                  |
| Missing                                                                        | 1,105 (76.8%)                 | 4,421 (72.1%)           | 685 (74.1%)                  | 6,211 (73.1%)                |
| <b>History of smoking, n (%)</b>                                               |                               |                         |                              |                              |
| Never                                                                          | 758 (52.7%)                   | 3,159 (51.5%)           | 506 (54.7%)                  | 4,423 (52.1%)                |
| Ever                                                                           | 551 (38.3%)                   | 2,535 (41.3%)           | 352 (38.1%)                  | 3,438 (40.5%)                |
| Missing                                                                        | 130 (9.0%)                    | 437 (7.1%)              | 67 (7.2%)                    | 634 (7.5%)                   |
| <b>AJCC stage, n (%)</b>                                                       |                               |                         |                              |                              |
| Stage I                                                                        | 1,022 (71.0%)                 | 3,542 (57.8%)           | 605 (65.4%)                  | 5,169 (60.8%)                |
| Stage II                                                                       | 311 (21.6%)                   | 2,041 (33.3%)           | 260 (28.1%)                  | 2,612 (30.7%)                |
| Stage III                                                                      | 106 (7.4%)                    | 548 (8.9%)              | 60 (6.5%)                    | 714 (8.4%)                   |
| <b>AI type, n (%)</b>                                                          |                               |                         |                              |                              |
| Anastrozole                                                                    | -                             | 5,776 (94.2%)           | -                            | -                            |
| Letrozole                                                                      | -                             | 541 (8.8%)              | -                            | -                            |
| Exemestane                                                                     | -                             | 187 (3.1%)              | -                            | -                            |

|                                            |           |               |               |             |               |
|--------------------------------------------|-----------|---------------|---------------|-------------|---------------|
| <b>Received chemotherapy, n (%)</b>        |           |               |               |             |               |
|                                            | No        | 1,178 (81.9%) | 4,259 (69.5%) | 690 (74.6%) | 6,127 (72.1%) |
|                                            | Yes       | 248 (17.2%)   | 1,847 (30.1%) | 234 (25.3%) | 2,329 (27.4%) |
|                                            | Missing   | 13 (0.9%)     | 25 (0.4%)     | 1 (0.1%)    | 39 (0.5%)     |
| <b>Received radiation, n (%)</b>           |           |               |               |             |               |
|                                            | No        | 892 (62.0%)   | 3,087 (50.4%) | 479 (51.8%) | 4,458 (52.5%) |
|                                            | Yes       | 504 (35.0%)   | 2,990 (48.8%) | 427 (46.2%) | 3,921 (46.2%) |
|                                            | Missing   | 43 (3.0%)     | 54 (0.9%)     | 19 (2.1%)   | 116 (1.4%)    |
| <b>COPS2</b>                               |           |               |               |             |               |
|                                            | Cops2     |               |               |             |               |
|                                            | Mean (SD) | 17.7 (19.3)   | 14.4 (15.3)   | 14.4 (16.0) | 15.0 (16.1)   |
|                                            | Missing   | 43 (3.0%)     | 54 (0.9%)     | 19 (2.1%)   | 116 (1.4%)    |
| <b>Depression, n (%)</b>                   |           |               |               |             |               |
|                                            | No        | 254 (17.7%)   | 1,289 (21.0%) | 189 (20.4%) | 1,732 (20.4%) |
|                                            | Yes       | 66 (4.6%)     | 378 (6.2%)    | 48 (5.2%)   | 492 (5.8%)    |
|                                            | Missing   | 1,119 (77.8%) | 4,464 (72.8%) | 688 (74.4%) | 6,271 (73.8%) |
| <b>History of prior CVD, Yes, n (%)</b>    |           | 212 (14.7%)   | 647 (10.6%)   | 82 (8.9%)   | 941 (11.1%)   |
| <b>History of diabetes, Yes, n (%)</b>     |           | 354 (24.6%)   | 1,604 (26.2%) | 178 (19.2%) | 2,136 (25.1%) |
| <b>History of dyslipidemia, Yes, n (%)</b> |           | 920 (63.9%)   | 4,228 (69.0%) | 514 (55.6%) | 5,662 (66.7%) |
| <b>History of hypertension, Yes, n (%)</b> |           | 994 (69.1%)   | 4,295 (70.1%) | 562 (60.8%) | 5,851 (68.9%) |

Abbreviations: AI = Aromatase Inhibitor, AJCC = American Joint Committee on Cancer, BMI = Body Mass Index, COPS2 = Comorbidity Point Score Version 2, CVD = Cardiovascular Disease, SD = Standard Deviation

Definition of BMI category: Underweight: BMI less than 18.5 kg/m<sup>2</sup>; Normal: BMI 18.5 to <25 kg/m<sup>2</sup>; Overweight: BMI 25.0 to <30 kg/m<sup>2</sup>; Obese: BMI 30 or higher kg/m<sup>2</sup>.

Note: endocrine therapy was defined at the landmark time, i.e., 12 months after breast cancer diagnosis.

**Table 2. Associations of endocrine therapy use at 12 months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD Outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Non-user  | 100           | 32                     | 1224                | Ref               |
|                        | AI        | 395           | 87                     | 5528                | 0.86 [0.68, 1.08] |
|                        | Tamoxifen | 52            | 13                     | 822                 | 0.98 [0.70, 1.38] |
| Stroke                 | Non-user  | 58            | 11                     | 1245                | Ref               |
|                        | AI        | 221           | 19                     | 5596                | 1.02 [0.76, 1.39] |
|                        | Tamoxifen | 27            | 6                      | 829                 | 0.94 [0.59, 1.49] |
| Heart Failure          | Non-user  | 138           | 41                     | 1215                | Ref               |
|                        | AI        | 460           | 69                     | 5546                | 0.79 [0.65, 0.97] |
|                        | Tamoxifen | 62            | 8                      | 827                 | 0.90 [0.66, 1.22] |
| MACE                   | Non-user  | 270           | 87                     | 1169                | Ref               |
|                        | AI        | 980           | 166                    | 5449                | 0.84 [0.73, 0.97] |
|                        | Tamoxifen | 139           | 26                     | 809                 | 0.96 [0.78, 1.18] |
| Mortality Outcomes     |           |               |                        |                     |                   |
| All Death              | Non-user  | 525           | 45                     | 1211                | Ref               |
|                        | AI        | 1554          | 31                     | 5584                | 0.74 [0.67, 0.82] |
|                        | Tamoxifen | 226           | 7                      | 828                 | 0.82 [0.70, 0.96] |
| CVD Death              | Non-user  | 137           | 11                     | 1245                | Ref               |
|                        | AI        | 354           | 7                      | 5608                | 0.73 [0.59, 0.91] |
|                        | Tamoxifen | 62            | 2                      | 833                 | 0.97 [0.72, 1.32] |
| Non-CVD Death          | Non-user  | 388           | 34                     | 1222                | Ref               |
|                        | AI        | 1200          | 24                     | 5591                | 0.74 [0.66, 0.84] |
|                        | Tamoxifen | 164           | 5                      | 830                 | 0.77 [0.64, 0.93] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 3. Effect modification of general obesity on the associations of endocrine therapy use at 12months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

|                        |           | Normal BMI    |                        |                     |                   | Overweight or Obese BMI |                        |                     |                   |                   |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|-------------------------|------------------------|---------------------|-------------------|-------------------|
| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       | No. of events           | No. of excluded events | No. of participants | HR (95% CI)       | P for interaction |
|                        |           |               |                        |                     |                   |                         |                        |                     |                   |                   |
| CVD outcomes           |           |               |                        |                     |                   |                         |                        |                     |                   |                   |
| Ischemic Heart Disease | Non-user  | 29            | 12                     | 429                 | Ref               | 71                      | 20                     | 795                 | Ref               | Ref               |
|                        | AI        | 84            | 17                     | 1530                | 0.86 [0.55, 1.33] | 311                     | 70                     | 3997                | 0.86 [0.66, 1.13] | 0.93              |
|                        | Tamoxifen | 16            | 2                      | 301                 | 1.01 [0.54, 1.87] | 36                      | 11                     | 519                 | 0.99 [0.66, 1.48] | 0.98              |
| Stroke                 | Non-user  | 21            | 4                      | 437                 | Ref               | 37                      | 7                      | 808                 | Ref               | Ref               |
|                        | AI        | 69            | 4                      | 1543                | 1.11 [0.66, 1.86] | 152                     | 15                     | 4052                | 1.00 [0.69, 1.46] | 0.61              |
|                        | Tamoxifen | 9             | 4                      | 299                 | -                 | 18                      | 2                      | 528                 | -                 | -                 |
| Heart Failure          | Non-user  | 37            | 10                     | 431                 | Ref               | 101                     | 31                     | 784                 | Ref               | Ref               |
|                        | AI        | 89            | 11                     | 1536                | 0.81 [0.54, 1.21] | 371                     | 58                     | 4009                | 0.83 [0.65, 1.04] | 0.90              |
|                        | Tamoxifen | 14            | 0                      | 303                 | 0.69 [0.37, 1.29] | 48                      | 8                      | 522                 | 0.97 [0.69, 1.38] | 0.36              |
| MACE                   | Non-user  | 90            | 26                     | 415                 | Ref               | 180                     | 61                     | 754                 | Ref               | Ref               |
|                        | AI        | 242           | 29                     | 1518                | 0.87 [0.68, 1.13] | 738                     | 137                    | 3930                | 0.83 [0.70, 0.98] | 0.74              |
|                        | Tamoxifen | 45            | 5                      | 298                 | 0.97 [0.68, 1.40] | 94                      | 21                     | 509                 | 0.94 [0.73, 1.22] | 0.96              |
| Mortality outcomes     |           |               |                        |                     |                   |                         |                        |                     |                   |                   |
| All Death              | Non-user  | 212           | 13                     | 428                 | Ref               | 313                     | 32                     | 783                 | Ref               | Ref               |
|                        | AI        | 441           | 11                     | 1536                | 0.71 [0.60, 0.84] | 1113                    | 20                     | 4047                | 0.77 [0.68, 0.88] | 0.20              |
|                        | Tamoxifen | 74            | 2                      | 301                 | 0.66 [0.51, 0.87] | 151                     | 5                      | 525                 | 0.91 [0.75, 1.11] | 0.02              |
| CVD Death              | Non-user  | 53            | 3                      | 438                 | Ref               | 84                      | 8                      | 807                 | Ref               | Ref               |
|                        | AI        | 102           | 1                      | 1546                | 0.79 [0.55, 1.12] | 252                     | 6                      | 4061                | 0.72 [0.55, 0.93] | 0.81              |
|                        | Tamoxifen | 23            | 0                      | 303                 | 0.98 [0.59, 1.62] | 39                      | 2                      | 528                 | 0.97 [0.66, 1.42] | 0.66              |
| Non-CVD Death          | Non-user  | 159           | 10                     | 431                 | Ref               | 229                     | 24                     | 791                 | Ref               | Ref               |
|                        | AI        | 339           | 10                     | 1537                | 0.68 [0.56, 0.83] | 861                     | 14                     | 4053                | 0.80 [0.68, 0.93] | 0.14              |

|           |    |   |     |                   |     |   |     |                   |      |
|-----------|----|---|-----|-------------------|-----|---|-----|-------------------|------|
| Tamoxifen | 51 | 2 | 301 | 0.57 [0.42, 0.79] | 112 | 3 | 527 | 0.90 [0.71, 1.13] | 0.01 |
|-----------|----|---|-----|-------------------|-----|---|-----|-------------------|------|

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), history of ever smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 4. Effect modification of central obesity on the associations of endocrine therapy use at 12 months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

|                           |           | Waist circumference ≤ 95.2 cm |                              |                            |                   | Waist circumference > 95.2 cm |                              |                            |                   |                          |
|---------------------------|-----------|-------------------------------|------------------------------|----------------------------|-------------------|-------------------------------|------------------------------|----------------------------|-------------------|--------------------------|
| Outcome                   | Group     | No. of<br>event<br>s          | No. of<br>excluded<br>events | No. of<br>participan<br>ts | HR (95% CI)       | No. of<br>events              | No. of<br>excluded<br>events | No. of<br>participa<br>nts | HR (95% CI)       | P for<br>interactio<br>n |
| CVD<br>outcomes           |           |                               |                              |                            |                   |                               |                              |                            |                   |                          |
| Ischemic<br>Heart Disease | Non-user  | 12                            | 3                            | 181                        | Ref               | 14                            | 4                            | 137                        | Ref               | Ref                      |
|                           | AI        | 39                            | 13                           | 785                        | 0.94 [0.46, 1.91] | 76                            | 17                           | 879                        | 0.74 [0.41, 1.35] | 0.44                     |
|                           | Tamoxifen | 10                            | 0                            | 142                        | -                 | 5                             | 5                            | 90                         | -                 | -                        |
| Stroke                    | Non-user  | 9                             | 2                            | 182                        | Ref               | 3                             | 0                            | 141                        | Ref               | Ref                      |
|                           | AI        | 20                            | 1                            | 797                        | -                 | 43                            | 3                            | 893                        | -                 | -                        |
|                           | Tamoxifen | 6                             | 0                            | 142                        | -                 | 4                             | 1                            | 94                         | -                 | -                        |
| Heart Failure             | Non-user  | 12                            | 3                            | 181                        | Ref               | 20                            | 3                            | 138                        | Ref               | Ref                      |
|                           | AI        | 47                            | 4                            | 794                        | 1.43 [0.71, 2.89] | 90                            | 16                           | 880                        | 0.59 [0.35, 0.97] | 0.09                     |
|                           | Tamoxifen | 8                             | 0                            | 142                        | -                 | 10                            | 1                            | 94                         | -                 | -                        |
| MACE                      | Non-user  | 29                            | 7                            | 177                        | Ref               | 35                            | 8                            | 133                        | Ref               | Ref                      |
|                           | AI        | 101                           | 17                           | 781                        | 1.22 [0.78, 1.91] | 175                           | 35                           | 861                        | 0.65 [0.44, 0.96] | 0.06                     |
|                           | Tamoxifen | 22                            | 0                            | 142                        | 1.37 [0.77, 2.45] | 17                            | 5                            | 90                         | 0.78 [0.43, 1.42] | 0.38                     |
| Mortality<br>outcomes     |           |                               |                              |                            |                   |                               |                              |                            |                   |                          |
| All Death                 | Non-user  | 67                            | 1                            | 183                        | Ref               | 52                            | 2                            | 139                        | Ref               | Ref                      |
|                           | AI        | 179                           | 2                            | 796                        | 0.83 [0.61, 1.13] | 272                           | 4                            | 892                        | 0.76 [0.56, 1.04] | 0.95                     |
|                           | Tamoxifen | 24                            | 1                            | 141                        | 0.59 [0.36, 0.95] | 24                            | 1                            | 94                         | 0.85 [0.52, 1.40] | 0.13                     |
| CVD Death                 | Non-user  | 17                            | 1                            | 183                        | Ref               | 12                            | 1                            | 140                        | Ref               | Ref                      |
|                           | AI        | 32                            | 0                            | 798                        | 0.79 [0.41, 1.54] | 75                            | 1                            | 895                        | 0.94 [0.50, 1.76] | 0.22                     |
|                           | Tamoxifen | 8                             | 0                            | 142                        | -                 | 4                             | 0                            | 95                         | -                 | -                        |
| Non-CVD<br>Death          | Non-user  | 50                            | 0                            | 184                        | Ref               | 40                            | 1                            | 140                        | Ref               | Ref                      |
|                           | AI        | 147                           | 2                            | 796                        | 0.85 [0.60, 1.20] | 197                           | 3                            | 893                        | 0.72 [0.50, 1.02] | 0.62                     |
|                           | Tamoxifen | 16                            | 1                            | 141                        | 0.49 [0.28, 0.87] | 20                            | 1                            | 94                         | 0.95 [0.55, 1.66] | 0.09                     |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 5. Effect modification of depression on the associations of endocrine therapy use at 12months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

|                        |           | Depression     |                         |                      |                   | No depression |                         |                      |                   |                    |
|------------------------|-----------|----------------|-------------------------|----------------------|-------------------|---------------|-------------------------|----------------------|-------------------|--------------------|
| Outcome                | Group     | No. of event s | No. of exclud ed events | No. of participa nts | HR (95% CI)       | No. of events | No. of exclud ed events | No. of particip ants | HR (95% CI)       | P for intera ction |
| CVD outcomes           |           |                |                         |                      |                   |               |                         |                      |                   |                    |
| Ischemic Heart Disease | Non-user  | 4              | 1                       | 65                   | Ref               | 20            | 5                       | 242                  | Ref               | Ref                |
|                        | AI        | 27             | 8                       | 369                  | -                 | 88            | 19                      | 1253                 | -                 | -                  |
|                        | Tamoxifen | 3              | 1                       | 46                   | -                 | 9             | 4                       | 183                  | -                 | -                  |
| Stroke                 | Non-user  | 2              | 1                       | 65                   | Ref               | 10            | 2                       | 245                  | Ref               | Ref                |
|                        | AI        | 11             | 1                       | 376                  | -                 | 48            | 3                       | 1269                 | -                 | -                  |
|                        | Tamoxifen | 0              | 1                       | 46                   | -                 | 10            | 0                       | 187                  | -                 | -                  |
| Heart Failure          | Non-user  | 5              | 3                       | 63                   | Ref               | 25            | 4                       | 243                  | Ref               | Ref                |
|                        | AI        | 33             | 5                       | 372                  | -                 | 103           | 17                      | 1255                 | -                 | -                  |
|                        | Tamoxifen | 4              | 1                       | 46                   | -                 | 12            | 1                       | 186                  | -                 | -                  |
| MACE                   | Non-user  | 12             | 4                       | 62                   | Ref               | 50            | 12                      | 235                  | Ref               | Ref                |
|                        | AI        | 62             | 12                      | 365                  | 0.95 [0.48, 1.85] | 206           | 39                      | 1233                 | 0.85 [0.62, 1.18] | 0.89               |
|                        | Tamoxifen | 5              | 2                       | 45                   | -                 | 31            | 4                       | 183                  | -                 | -                  |
| Mortality outcomes     |           |                |                         |                      |                   |               |                         |                      |                   | Ref                |
| All Death              | Non-user  | 20             | 0                       | 66                   | Ref               | 98            | 3                       | 244                  | Ref               |                    |
|                        | AI        | 101            | 0                       | 377                  | 0.85 [0.51, 1.43] | 337           | 6                       | 1266                 | 0.69 [0.54, 0.87] | 0.27               |
|                        | Tamoxifen | 6              | 1                       | 46                   | -                 | 39            | 1                       | 186                  | -                 | -                  |
| CVD Death              | Non-user  | 4              | 0                       | 66                   | Ref               | 27            | 2                       | 245                  | Ref               | Ref                |
|                        | AI        | 21             | 0                       | 377                  | -                 | 81            | 1                       | 1271                 | -                 | -                  |
|                        | Tamoxifen | 1              | 0                       | 47                   | -                 | 12            | 0                       | 187                  | -                 | -                  |
| Non-CVD Death          | Non-user  | 16             | 0                       | 66                   | Ref               | 71            | 1                       | 246                  | Ref               | Ref                |
|                        | AI        | 80             | 0                       | 377                  | 0.89 [0.50, 1.58] | 256           | 5                       | 1267                 | 0.69 [0.53, 0.91] | 0.34               |
|                        | Tamoxifen | 5              | 1                       | 46                   | -                 | 27            | 1                       | 186                  | -                 | -                  |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 6. Effect modification of CVD history on the associations of endocrine therapy use at 12months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

| Outcome                | Group     | Had CVD history |                        |                     |                   | No CVD history |                        |                     |                   | P for interaction |
|------------------------|-----------|-----------------|------------------------|---------------------|-------------------|----------------|------------------------|---------------------|-------------------|-------------------|
|                        |           | No. of events   | No. of excluded events | No. of participants | HR (95% CI)       | No. of events  | No. of excluded events | No. of participants | HR (95% CI)       |                   |
| CVD outcomes           |           |                 |                        |                     |                   |                |                        |                     |                   |                   |
| Ischemic Heart Disease | Non-user  | 36              | 19                     | 171                 | Ref               | 64             | 13                     | 1053                | Ref               | Ref               |
|                        | AI        | 106             | 62                     | 528                 | 0.77 [0.51, 1.15] | 289            | 25                     | 5000                | 0.90 [0.68, 1.18] | 0.57              |
|                        | Tamoxifen | 20              | 8                      | 65                  | 1.43 [0.82, 2.49] | 32             | 5                      | 757                 | 0.82 [0.54, 1.27] | 0.18              |
| Stroke                 | Non-user  | 15              | 3                      | 187                 | Ref               | 43             | 8                      | 1058                | Ref               | Ref               |
|                        | AI        | 45              | 5                      | 585                 | 1.06 [0.56, 1.98] | 176            | 14                     | 5011                | 1.01 [0.71, 1.42] | 0.97              |
|                        | Tamoxifen | 5               | 1                      | 72                  | -                 | 22             | 5                      | 757                 | -                 | -                 |
| Heart Failure          | Non-user  | 41              | 32                     | 158                 | Ref               | 97             | 9                      | 1057                | Ref               | Ref               |
|                        | AI        | 138             | 45                     | 545                 | 0.99 [0.68, 1.44] | 322            | 24                     | 5001                | 0.72 [0.56, 0.91] | 0.20              |
|                        | Tamoxifen | 16              | 4                      | 69                  | 0.91 [0.51, 1.64] | 46             | 4                      | 758                 | 0.87 [0.61, 1.24] | 0.87              |
| MACE                   | Non-user  | 64              | 51                     | 139                 | Ref               | 206            | 36                     | 1030                | Ref               | Ref               |
|                        | AI        | 222             | 104                    | 486                 | 0.96 [0.71, 1.29] | 758            | 62                     | 4963                | 0.79 [0.68, 0.93] | 0.26              |
|                        | Tamoxifen | 32              | 12                     | 61                  | 1.11 [0.72, 1.71] | 107            | 14                     | 748                 | 0.91 [0.72, 1.15] | 0.48              |
| Mortality outcomes     |           |                 |                        |                     |                   |                |                        |                     |                   |                   |
| All Death              | Non-user  | 131             | 10                     | 180                 | Ref               | 394            | 35                     | 1031                | Ref               | Ref               |
|                        | AI        | 300             | 10                     | 580                 | 0.82 [0.66, 1.02] | 1254           | 21                     | 5004                | 0.73 [0.65, 0.82] | 0.73              |
|                        | Tamoxifen | 38              | 0                      | 73                  | 0.84 [0.58, 1.22] | 188            | 7                      | 755                 | 0.81 [0.68, 0.97] | 0.95              |
| CVD Death              | Non-user  | 43              | 3                      | 187                 | Ref               | 94             | 8                      | 1058                | Ref               | Ref               |
|                        | AI        | 95              | 3                      | 587                 | 0.81 [0.55, 1.20] | 259            | 4                      | 5021                | 0.70 [0.54, 0.90] | 0.51              |
|                        | Tamoxifen | 12              | 0                      | 73                  | 0.76 [0.40, 1.47] | 50             | 2                      | 760                 | 1.02 [0.72, 1.45] | 0.46              |
| Non-CVD Death          | Non-user  | 88              | 7                      | 183                 | Ref               | 300            | 27                     | 1039                | Ref               | Ref               |
|                        | AI        | 205             | 7                      | 583                 | 0.81 [0.62, 1.07] | 995            | 17                     | 5008                | 0.74 [0.65, 0.85] | 0.97              |
|                        | Tamoxifen | 26              | 0                      | 73                  | 0.84 [0.54, 1.31] | 138            | 5                      | 757                 | 0.76 [0.62, 0.93] | 0.84              |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

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CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 1. Standard codes for the ascertainment of non-fatal and fatal major cardiovascular events in the Pathways Heart Study**

|                                                           | <b>Primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis or Procedure Codes</b> | <b>Primary International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis or Procedure Codes</b>                                                                                                                                         | <b>Current Procedural Terminology (CPT4®) Codes for Medical Billing Services</b> |
|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| <b>Ischemic Heart Disease</b>                             |                                                                                                                                        |                                                                                                                                                                                                                                                                                 |                                                                                  |
| 1. Acute myocardial infarction                            | 410.X                                                                                                                                  | I21.01, I21.02, I21.3, I21.4, I21.09, I21.11, I21.19, I21.21, I21.29, I22.0, I22.1, I22.2, I22.8, I22.9                                                                                                                                                                         | Not applicable                                                                   |
| 2. Other acute & subacute forms of ischemic heart disease | 411.X                                                                                                                                  | I20.0, I24.0, I24.1, I24.8, I24.9, I25.720, I25.750, I25.760, I25.790                                                                                                                                                                                                           | Not applicable                                                                   |
| 3. Angina pectoris                                        | 413.X                                                                                                                                  | I20.1, I20.8, I20.9, I25.110, I25.111, I25.118, I25.119, I25.701, I25.708, I25.709, I25.711, I25.718, I25.719, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.751, I25.758, I25.759, I25.761, I25.768, I25.769, I25.700, I25.710, I25.791, I25.798, I25.799 | Not applicable                                                                   |
| 4. Other ischemic heart disease                           | 414<br>414.8<br>414.9                                                                                                                  | I25.10, I25.110, I25.5, I25.6, I25.701, I25.711, I25.720, I25.721, I25.728, I25.729, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.89, I25.9            | Not applicable                                                                   |
| 5. Aortocoronary bypass status convert                    | V45.81                                                                                                                                 | Z95.1                                                                                                                                                                                                                                                                           | Not applicable                                                                   |

|                                                          |                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                        |
|----------------------------------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6. Percutaneous transluminal coronary angioplasty status | V45.82                                                                                | Z95.5, Z98.61                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Not applicable                                                                                                                                         |
| 7. Coronary artery bypass surgery (CABG)                 | 36.1<br>36.11<br>36.12<br>36.13<br>36.14<br>36.15<br>36.16<br>36.17<br>36.19<br>36.03 | 0210083, 0210088, 0210089, 021008C,<br>021008F, 021008W, 0210093, 0210098,<br>0210099, 021009C, 021009F, 021009W,<br>02100A3, 02100A8, 02100A9, 02100AC,<br>02100AF, 02100AW, 02100J3, 02100J8,<br>02100J9, 02100JC, 02100JF, 02100JW,<br>02100K3, 02100K8, 02100K9, 02100KC,<br>02100KF, 02100KW, 02100Z3, 02100Z8,<br>02100Z9, 02100ZC, 02100ZF, 0210483,<br>0210488, 0210489, 021048C, 021048F,<br>021048W, 0210493, 0210498, 0210499,<br>021049C, 021049F, 021049W, 02104A3,<br>02104A8, 02104A9, 02104AC, 02104AF,<br>02104AW, 02104J3, 02104J8, 02104J9,<br>02104JC, 02104JF, 02104JW, 02104K3,<br>02104K8, 02104K9, 02104KC, 02104KF,<br>02104KW, 02104Z3, 02104Z8, 02104Z9,<br>02104ZC, 02104ZF, 0211083, 0211088,<br>0211089, 021108C, 021108F, 021108W,<br>0211093, 0211098, 0211099, 021109C,<br>021109F, 021109W, 02110A3, 02110A8,<br>02110A9, 02110AC, 02110AF, 02110AW,<br>02110J3, 02110J8, 02110J9, 02110JC,<br>02110JF, 02110JW, 02110K3, 02110K8,<br>02110K9, 02110KC, 02110KF, 02110KW,<br>02110Z3, 02110Z8, 02110Z9, 02110ZC,<br>02110ZF, 0211483, 0211488, 0211489,<br>021148C, 021148F, 021148W, 0211493,<br>0211498, 0211499, 021149C, 021149F,<br>021149W, 02114A3, 02114A8, 02114A9,<br>02114AC, 02114AF, 02114AW, 02114J3,<br>02114J8, 02114J9, 02114JC, 02114JF,<br>02114JW, 02114K3, 02114K8, 02114K9,<br>02114KC, 02114KF, 02114KW, 02114Z3, | 33510, 33511, 33512, 33513,<br>33514, 33515, 33516, 33517,<br>33518, 33519, 33520, 33521,<br>33522, 33523, 33525, 33530,<br>33533, 33534, 33535, 33536 |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | 02114Z8, 02114Z9, 02114ZC, 02114ZF,<br>0212083, 0212088, 0212089, 021208C,<br>021208F, 021208W, 0212093, 0212098,<br>0212099, 021209C, 021209F, 021209W,<br>02120A3, 02120A8, 02120A9, 02120AC,<br>02120AF, 02120AW, 02120J3, 02120J8,<br>02120J9, 02120JC, 02120JF, 02120JW,<br>02120K3, 02120K8, 02120K9, 02120KC,<br>02120KF, 02120KW, 02120Z3, 02120Z8,<br>02120Z9, 02120ZC, 02120ZF, 0212483,<br>0212488, 0212489, 021248C, 021248F,<br>021248W, 0212493, 0212498, 0212499,<br>021249C, 021249F, 021249W, 02124A3,<br>02124A8, 02124A9, 02124AC, 02124AF,<br>02124AW, 02124J3, 02124J8, 02124J9,<br>02124JC, 02124JF, 02124JW, 02124K3,<br>02124K8, 02124K9, 02124KC, 02124KF,<br>02124KW, 02124Z3, 02124Z8, 02124Z9,<br>02124ZC, 02124ZF, 0213083, 0213088,<br>0213089, 021308C, 021308F, 021308W,<br>0213093, 0213098, 0213099, 021309C,<br>021309F, 021309W, 02130A3, 02130A8,<br>02130A9, 02130AC, 02130AF, 02130AW,<br>02130J3, 02130J8, 02130J9, 02130JC,<br>02130JF, 02130JW, 02130K3, 02130K8,<br>02130K9, 02130KC, 02130KF, 02130KW,<br>02130Z3, 02130Z8, 02130Z9, 02130ZC,<br>02130ZF, 0213483, 0213488, 0213489,<br>021348C, 021348F, 021348W, 0213493,<br>0213498, 0213499, 021349C, 021349F,<br>021349W, 02134A3, 02134A8, 02134A9,<br>02134AC, 02134AF, 02134AW, 02134J3,<br>02134J8, 02134J9, 02134JC, 02134JF,<br>02134JW, 02134K3, 02134K8, 02134K9,<br>02134KC, 02134KF, 02134KW, 02134Z3,<br>02134Z8, 02134Z9, 02134ZC, 02134ZF, |  |
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|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |  |
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|  |  | 0270046, 0270056, 027005Z, 0270066,<br>027006Z, 0270076, 027007Z, 02700D6,<br>02700DZ, 02700E6, 02700EZ, 02700F6,<br>02700FZ, 02700G6, 02700GZ, 02700T6,<br>02700TZ, 02700Z6, 02700ZZ, 0271046,<br>027104Z, 0271056, 027105Z, 0271066,<br>027106Z, 0271076, 027107Z, 02710D6,<br>02710DZ, 02710E6, 02710EZ, 02710F6,<br>02710FZ, 02710G6, 02710GZ, 02710T6,<br>02710TZ, 02710Z6, 02710ZZ, 0272046,<br>027204Z, 0272056, 027205Z, 0272066,<br>027206Z, 0272076, 027207Z, 02720D6,<br>02720DZ, 02720E6, 02720EZ, 02720F6,<br>02720FZ, 02720G6, 02720GZ, 02720T6,<br>02720TZ, 02720Z6, 02720ZZ, 0273046,<br>027304Z, 0273056, 027305Z, 0273066,<br>027306Z, 0273076, 027307Z, 02730D6,<br>02730DZ, 02730E6, 02730EZ, 02730F6,<br>02730FZ, 02730G6, 02730GZ, 02730T6,<br>02730TZ, 02730Z6, 02730ZZ, 02C00Z6,<br>02C00ZZ, 02C10Z6, 02C10ZZ, 02C20Z6,<br>02C20ZZ, 02C30Z6, 02C30ZZ |  |
|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

|                                                          |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                       |
|----------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| <p>8. Percutaneous transluminal coronary angioplasty</p> | <p>0.66</p> | <p>0270376, 02703D6, 02703E6, 02703EZ, 02703F6, 02703FZ, 02703G6, 02703GZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 0270446, 0270456, 027045Z, 0270466, 027046Z, 0270476, 027047Z, 02704D6, 02704DZ, 02704E6, 02704EZ, 02704F6, 02704FZ, 02704G6, 02704GZ, 02704T6, 02704TZ, 02704Z6, 02704ZZ, 02713D6, 02713DZ, 02713E6, 02713EZ, 02713F6, 02713FZ, 02713G6, 02713GZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 0271446, 027144Z, 0271456, 027145Z, 0271466, 027146Z, 0271476, 027147Z, 02714D6, 02714DZ, 02714E6, 02714EZ, 02714F6, 02714FZ, 02714G6, 02714GZ, 02714T6, 02714TZ, 02714Z6, 02714ZZ, 0272346, 027235Z, 0272366, 0272376, 02723D6, 02723DZ, 02723E6, 02723EZ, 02723F6, 02723FZ, 02723G6, 02723GZ, 02723T6, 02723TZ, 02723Z6, 02723ZZ, 0272446, 027244Z, 0272456, 027245Z, 0272466, 027246Z, 0272476, 027247Z, 02724D6, 02724DZ, 02724E6, 02724EZ, 02724F6, 02724FZ, 02724G6, 02724GZ, 02724T6, 02724TZ, 02724Z6, 02724ZZ, 0273356, 027335Z, 0273366, 02733D6, 02733DZ, 02733E6, 02733EZ, 02733F6, 02733FZ, 02733G6, 02733GZ, 02733T6, 02733TZ, 02733Z6, 02733ZZ, 0273446, 027344Z, 0273456, 027345Z, 0273466, 027346Z, 0273476, 027347Z, 02734D6, 02734DZ, 02734E6, 02734EZ, 02734F6, 02734FZ, 02734G6, 02734GZ, 02734T6, 02734TZ, 02734Z6, 02734ZZ</p> | <p>Not applicable</p> |
|----------------------------------------------------------|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|

|                                                                                            |                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                        |
|--------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <p>9. Percutaneous coronary intervention (PCI) with or without intra-coronary stenting</p> | <p>36.01, 36.02, 36.05, 36.06, 36.07, 36.09</p> | <p>0270046, 027004Z, 0270056, 027005Z, 0270066, 027006Z, 0270076, 027007Z, 02700D6, 02700DZ, 02700E6, 02700EZ, 02700F6, 02700FZ, 02700G6, 02700GZ, 02700T6, 02700TZ, 0270346, 027034Z, 0270356, 027035Z, 0270366, 027036Z, 0270376, 027037Z, 02703D6, 02703DZ, 02703E6, 02703EZ, 02703F6, 02703FZ, 02703G6, 02703GZ, 02703T6, 02703TZ, 0270446, 027044Z, 0270456, 027045Z, 0270466, 027046Z, 0270476, 027047Z, 02704D6, 02704DZ, 02704E6, 02704EZ, 02704F6, 02704FZ, 02704G6, 02704GZ, 02704T6, 02704TZ, 0271046, 027104Z, 0271056, 027105Z, 0271066, 027106Z, 0271076, 027107Z, 02710D6, 02710DZ, 02710E6, 02710EZ, 02710F6, 02710FZ, 02710G6, 02710GZ, 02710T6, 02710TZ, 0271346, 027134Z, 0271356, 027135Z, 0271366, 027136Z, 0271376, 027137Z, 02713D6, 02713E6, 02713F6, 02713FZ, 02713G6, 02713GZ, 02713T6, 02713TZ, 0271446, 027144Z, 0271456, 027145Z, 0271466, 027146Z, 0271476, 027147Z, 02714D6, 02714DZ, 02714E6, 02714EZ, 02714F6, 02714FZ, 02714G6, 02714GZ, 02714T6, 02714TZ, 0272046, 027204Z, 0272056, 027205Z, 0272066, 027206Z, 0272076, 027207Z, 02720D6, 02720DZ, 02720E6, 02720EZ, 02720F6, 02720FZ, 02720G6, 02720GZ, 02720T6, 02720TZ, 0272346, 027234Z, 0272356, 027235Z, 0272366, 027236Z, 0272376, 027237Z, 02723D6, 02723DZ, 02723E6, 02723EZ, 02723FZ, 02723G6, 02723GZ, 02723T6, 02723TZ, 0272446, 027244Z, 0272456,</p> | <p>92973, 92980, 92981, 92982, 92984, 92995, 92996</p> |
|--------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|

|                                    |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |
|------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                    |                                                | 027245Z, 0272466, 027246Z, 0272476, 027247Z, 02724D6, 02724DZ, 02724E6, 02724EZ, 02724F6, 02724FZ, 02724G6, 02724GZ, 02724T6, 02724TZ, 0273046, 027304Z, 0273056, 027305Z, 0273066, 027306Z, 0273076, 027307Z, 02730D6, 02730DZ, 02730E6, 02730EZ, 02730F6, 02730FZ, 02730G6, 02730GZ, 02730T6, 02730TZ, 0273346, 027334Z, 0273356, 027335Z, 0273366, 027336Z, 0273376, 027337Z, 02733D6, 02733E6, 02733EZ, 02733F6, 02733FZ, 02733G6, 02733GZ, 02733T6, 02733TZ, 0273446, 027344Z, 0273456, 027345Z, 0273466, 027346Z, 0273476, 027347Z, 02734D6, 02734DZ, 02734E6, 02734EZ, 02734F6, 02734FZ, 02734G6, 02734GZ, 02734T6, 02734TZ, 02C03Z6, 02C03ZZ, 02C04Z6, 02C04ZZ, 02C13Z6, 02C13ZZ, 02C14Z6, 02C14ZZ, 02C23Z6, 02C23ZZ, 02C24Z6, 02C24ZZ, 02C33Z6, 02C33ZZ, 02C34Z6, 02C34ZZ |                |
| <b>Stroke, including TIA</b>       |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |
| 1. Transient Ischemic Attack (TIA) | 435.X                                          | G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, I67.841, I67.848                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Not applicable |
| 2. Acute Ischemic stroke           | 433.01<br>433.11<br>433.21<br>433.31<br>433.81 | I63.00, I63.02, I63.6, I63.8, I63.09, I63.9, I63.10, I63.011, I63.012, I63.12, I63.013, I63.019, I63.19, I63.20, I63.22, I63.29, I63.30, I63.031, I63.032, I63.033, I63.039, I63.39, I63.40, I63.49, I63.50, I63.59, I63.111, I63.112, I63.113, I63.119, I63.131,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Not applicable |

|                                  |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                |
|----------------------------------|---------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                  | 433.91<br>434.01<br>434.11<br>434.91<br>436 | I63.132, I63.133, I63.139, I63.211, I63.212, I63.213, I63.219, I63.231, I63.232, I63.233, I63.239, I63.311, I63.312, I63.313, I63.319, I63.321, I63.322, I63.323, I63.329, I63.331, I63.332, I63.333, I63.339, I63.341, I63.342, I63.343, I63.349, I63.411, I63.412, I63.413, I63.419, I63.421, I63.422, I63.423, I63.429, I63.431, I63.432, I63.433, I63.439, I63.441, I63.442, I63.443, I63.449, I63.511, I63.512, I63.513, I63.519, I63.521, I63.522, I63.523, I63.529, I63.531, I63.532, I63.533, I63.539, I63.541, I63.542, I63.543, I63.549, I67.89 |                |
| 3. Subarachnoid hemorrhage       | 430.X                                       | I60.00, I60.01, I60.02, I60.2, I60.4, I60.6, I60.7, I60.8, I60.9, I60.10, I60.11, I60.12, I60.30, I60.31, I60.32, I60.50, I60.51, I60.52                                                                                                                                                                                                                                                                                                                                                                                                                  | Not applicable |
| 4. Intracerebral hemorrhage      | 431.X                                       | I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Not applicable |
| 5. Retinal vascular occlusion    | 362.3                                       | G45.3, H34.00, H34.01, H34.02, H34.03, H34.9, H34.10, H34.11, H34.12, H34.13, H34.211, H34.212, H34.213, H34.219, H34.231, H34.232, H34.233, H34.239, H34.821, H34.822, H34.823, H34.829, H34.8110, H34.8111, H34.8112, H34.8120, H34.8121, H34.8122, H34.8130, H34.8131, H34.8132, H34.8190, H34.8191, H34.8192, H34.8310, H34.8311, H34.8312, H34.8320, H34.8321, H34.8322, H34.8330, H34.8331, H34.8332, H34.8390, H34.8391, H34.8392                                                                                                                  | Not applicable |
| 6. Other cerebrovascular disease | 437.X<br>438.X                              | G45.4, G46.3, G46.4, G46.5, G46.6, G46.7, G46.8, I67.1, I67.2, I67.4, I67.5, I67.6, I67.7, I67.9, I67.81, I67.82, I68.0, I68.2, I68.8, I69.00, I69.010, I69.10, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.020, I69.20, I69.021, I69.022, I69.023, I69.028, I69.30, I69.031, I69.032,                                                                                                                                                                                                                                             | Not applicable |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |  |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | I69.033, I69.034, I69.039, I69.041, I69.042,<br>I69.043, I69.044, I69.049, I69.051, I69.052,<br>I69.053, I69.054, I69.059, I69.061, I69.062,<br>I69.063, I69.064, I69.065, I69.069, I69.80,<br>I69.090, I69.90, I69.091, I69.092, I69.093,<br>I69.098, I69.110, I69.111, I69.112, I69.113,<br>I69.114, I69.115, I69.118, I69.119, I69.120,<br>I69.121, I69.122, I69.123, I69.128, I69.131,<br>I69.132, I69.133, I69.134, I69.139, I69.141,<br>I69.142, I69.143, I69.144, I69.149, I69.151,<br>I69.152, I69.153, I69.154, I69.159, I69.161,<br>I69.162, I69.163, I69.164, I69.165, I69.169,<br>I69.190, I69.191, I69.192, I69.193, I69.198,<br>I69.210, I69.211, I69.212, I69.213, I69.214,<br>I69.215, I69.218, I69.219, I69.220, I69.221,<br>I69.222, I69.223, I69.228, I69.231, I69.232,<br>I69.233, I69.234, I69.239, I69.241, I69.242,<br>I69.243, I69.244, I69.249, I69.251, I69.252,<br>I69.253, I69.254, I69.259, I69.261, I69.262,<br>I69.263, I69.264, I69.265, I69.269, I69.290,<br>I69.291, I69.292, I69.293, I69.298, I69.310,<br>I69.311, I69.312, I69.313, I69.314, I69.315,<br>I69.318, I69.319, I69.320, I69.321, I69.322,<br>I69.323, I69.328, I69.331, I69.332, I69.333,<br>I69.334, I69.339, I69.341, I69.342, I69.343,<br>I69.344, I69.349, I69.351, I69.352, I69.353,<br>I69.354, I69.359, I69.361, I69.362, I69.363,<br>I69.364, I69.365, I69.369, I69.390, I69.391,<br>I69.392, I69.393, I69.398, I69.810, I69.811,<br>I69.812, I69.813, I69.814, I69.815, I69.818,<br>I69.819, I69.820, I69.821, I69.822, I69.823,<br>I69.828, I69.831, I69.832, I69.833, I69.834,<br>I69.839, I69.841, I69.842, I69.843, I69.844,<br>I69.849, I69.851, I69.852, I69.853, I69.854,<br>I69.859, I69.861, I69.862, I69.863, I69.864,<br>I69.865, I69.869, I69.890, I69.891, I69.892, |  |
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|                                                |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                 |                |
|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                                |                                                                                                                                                                                                       | I69.893, I69.898, I69.910, I69.911, I69.912, I69.913, I69.914, I69.915, I69.918, I69.919, I69.920, I69.921, I69.922, I69.923, I69.928, I69.931, I69.932, I69.933, I69.934, I69.939, I69.941, I69.942, I69.943, I69.944, I69.949, I69.951, I69.952, I69.953, I69.954, I69.959, I69.961, I69.962, I69.963, I69.964, I69.965, I69.969, I69.990, I69.991, I69.992, I69.993, I69.998 |                |
| <b>Heart Failure, including Cardiomyopathy</b> |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                 |                |
| <b>1. Heart Failure</b>                        | 398.91, 402.01, 402.11, 402.91, 404.11, 404.13, 428.0, 428.1, 428.9<br>404.01, 404.03, 404.91, 404.93, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43 | I09.81, I11.0, I13.0, I13.2, I50, I50.1, I50.2, I50.20, I50.21, I50.22, I50.23, I50.3, I50.30, I50.31, I50.32, I50.33, I50.4, I50.40, I50.41, I50.42, I50.43,<br><br>I50.8, I50.81, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9, I97.13                                                                                                  | Not applicable |
| <b>2. Cardiomyopathy</b>                       | 425.2, 425.4, 425.5, 425.7, 425.8, 425.9                                                                                                                                                              | I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43,                                                                                                                                                                                                                                                                                                                                  | Not applicable |
| <b>Other CVD Outcomes</b>                      |                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                 |                |
| <b>Arrhythmia</b>                              | 426.0, 426.11, 426.12, 426.13, 426.3, 426.4, 426.6, 426.7, 427.0, 427.3X,                                                                                                                             | I44.0, I44.1, I44.2, I44.7, I45.0, I45.5, I45.6, I45.10, I45.19, I47.1, I48.0, I48.1, I48.2, I48.3, I48.4, I48.91, I48.92, I49.01, I49.1, I49.02, I49.2, I49.3, I49.5, I49.8, I49.9, I49.40, I49.49, R00.1                                                                                                                                                                      | Not applicable |

|                                      |                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                      | 427.4X, 427.6,<br>427.8X, 427.9                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                |
| <b>Venous thromboembolic disease</b> | 415.1<br>415.11<br>415.19<br>451.1<br>451.2<br>451.8, 451.81,<br>451.83, 451.84,<br>451.89<br>451.9<br>452<br>453<br>453.1<br>453.2<br>453.3<br>453.40, 453.41,<br>453.42<br>453.5, 453.51,<br>453.52<br>453.72, 453.73,<br>453.74, 453.75,<br>453.76, 453.77,<br>453.79<br>453.8, 453.82,<br>453.83, 453.84,<br>453.85, 453.86,<br>453.87, 453.89<br>453.9 | I26.01, I26.02, I26.09, I26.90, I26.92,<br>I26.99, I80.3, I80.8, I80.9, I80.10, I80.11,<br>I80.12, I80.13, I80.201, I80.202, I80.203,<br>I80.209, I80.211, I80.212, I80.213, I80.219,<br>I80.221, I80.222, I80.223, I80.229, I80.231,<br>I80.232, I80.233, I80.239, I80.291, I80.292,<br>I80.293, I80.299, I82.0, I82.1, I82.90,<br>I82.91, I82.210, I82.220, I82.221, I82.290,<br>I82.601, I82.602, I82.603, I82.609, I82.611,<br>I82.612, I82.613, I82.619, I82.621, I82.622,<br>I82.623, I82.629, I82.890, I82.A11,<br>I82.A12, I82.A13, I82.A19, I82.B11,<br>I82.B12, I82.B13, I82.B19, I82.C11,<br>I82.C12, I82.C13, I82.C19, T80.0XXA,<br>T81.72XA, T81.718A, T82.817A,<br>T82.818A | Not applicable |
| <b>Cardiac arrest</b>                | 427.5                                                                                                                                                                                                                                                                                                                                                       | I46.2, I46.8, I46.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                |
| <b>Myocarditis/Pericarditis</b>      | 422.0, 422.90,<br>422.91, 422.92,<br>422.93, 422.99,                                                                                                                                                                                                                                                                                                        | A18.84, I30.0, I30.1, I30.8, I30.9, I32,<br>I40.0, I40.1, I40.8, I40.9, I41, I51.4,<br>M32.12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Not applicable |

|                         |                                                            |                                                                                                                                                                               |                |
|-------------------------|------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                         | 429.0, 420.0,<br>420.90, 420.91,<br>420.99                 |                                                                                                                                                                               |                |
| <b>Valvular disease</b> | 424.0, 424.1,<br>424.2, 424.3<br>424.90, 424.91,<br>424.99 | A18.84, I34.0, I34.1, I34.2, I34.8, I34.9,<br>I35.0, I35.1, I35.2, I35.8, I35.9, I36.0,<br>I36.1, I36.2, I36.8, I36.9, I37.0, I37.1,<br>I37.2, I37.8, I37.9, I38, I39, M32.11 | Not applicable |
| <b>Carotid disease</b>  | 412.X<br>414.X                                             | I25.2, I25.3, I25.41, I25.42, I25.82, I25.83,<br>I25.84                                                                                                                       | Not applicable |

**Supplemental Table 2. Characteristics at breast cancer diagnosis in 1,210 non-users who did not have pharmacy claims of endocrine therapy**

|                                                                                | <b>Non-user<br/>(n=847)</b> | <b>User<br/>(n=121)</b>  | <b>No info/notes<br/>(n=242)</b> |
|--------------------------------------------------------------------------------|-----------------------------|--------------------------|----------------------------------|
| <b>Age at diagnosis, y, mean (SD)</b>                                          |                             |                          |                                  |
| Mean (SD)                                                                      | 72.5 (10.7)                 | 65.1 (11.7)              | 70.5 (11.8)                      |
| Median (Min, Max)                                                              | 73.0 (50.0, 100)            | 63.0 (29.0, 97.0)        | 70.0 (44.0, 98.0)                |
| <b>Race</b>                                                                    |                             |                          |                                  |
| Non-white                                                                      | 205 (24.2%)                 | 43 (35.5%)               | 73 (30.2%)                       |
| White                                                                          | 642 (75.8%)                 | 78 (64.5%)               | 169 (69.8%)                      |
| <b>Percent neighborhood education of college graduate or higher, Mean (SD)</b> |                             |                          |                                  |
| Mean (SD)                                                                      | 0.231 (0.115)               | 0.219 (0.113)            | 0.226 (0.123)                    |
| Median (Min, Max)                                                              | 0.224 (0, 0.677)            | 0.208 (0.0163, 0.470)    | 0.222 (0, 0.549)                 |
| Missing                                                                        | 24 (2.8%)                   | 0 (0%)                   | 17 (7.0%)                        |
| <b>Neighborhood median household income, \$, Mean (SD)</b>                     |                             |                          |                                  |
| Mean (SD)                                                                      | 78,100 (33,200)             | 77,900 (33,000)          | 73,300 (33,100)                  |
| Median (Min, Max)                                                              | 72,500 (15,500, 248,000)    | 74,900 (17,100, 180,000) | 67,300 (2,500, 180,000)          |
| Missing                                                                        | 24 (2.8%)                   | 0 (0%)                   | 17 (7.0%)                        |
| <b>BMI category</b>                                                            |                             |                          |                                  |
| Underweight                                                                    | 23 (2.7%)                   | 0 (0%)                   | 16 (6.6%)                        |
| Normal                                                                         | 307 (36.2%)                 | 42 (34.7%)               | 80 (33.1%)                       |
| Overweight                                                                     | 278 (32.8%)                 | 37 (30.6%)               | 69 (28.5%)                       |
| Obese                                                                          | 237 (28.0%)                 | 42 (34.7%)               | 74 (30.6%)                       |
| Missing                                                                        | 2 (0.2%)                    | 0 (0%)                   | 3 (1.2%)                         |
| <b>BMI, kg/m<sup>2</sup></b>                                                   |                             |                          |                                  |
| Mean (SD)                                                                      | 27.6 (6.38)                 | 28.3 (6.01)              | 27.5 (7.05)                      |
| Median (Min, Max)                                                              | 26.5 (14.5, 59.3)           | 27.4 (18.5, 46.6)        | 26.4 (14.3, 59.9)                |
| Missing                                                                        | 2 (0.2%)                    | 0 (0%)                   | 3 (1.2%)                         |
| <b>Waist circumference, cm</b>                                                 |                             |                          |                                  |
| Mean (SD)                                                                      | 92.5 (15.3)                 | 92.6 (14.8)              | 93.3 (17.5)                      |
| Median (Min, Max)                                                              | 90.9 (65.1, 144)            | 87.9 (69.9, 131)         | 93.1 (59.4, 129)                 |
| Missing                                                                        | 647 (76.4%)                 | 93 (76.9%)               | 197 (81.4%)                      |
| <b>History of smoking, n(%)</b>                                                |                             |                          |                                  |
| Never                                                                          | 442 (52.2%)                 | 58 (47.9%)               | 120 (49.6%)                      |
| Ever                                                                           | 345 (40.7%)                 | 48 (39.7%)               | 87 (36.0%)                       |
| Missing                                                                        | 60 (7.1%)                   | 15 (12.4%)               | 35 (14.5%)                       |
| <b>AJCC stage, n(%)</b>                                                        |                             |                          |                                  |
| Stage I                                                                        | 719 (84.9%)                 | 73 (60.3%)               | 145 (59.9%)                      |
| Stage II                                                                       | 107 (12.6%)                 | 39 (32.2%)               | 71 (29.3%)                       |

|                                           |             |            |             |
|-------------------------------------------|-------------|------------|-------------|
| Stage III                                 | 21 (2.5%)   | 9 (7.4%)   | 26 (10.7%)  |
| <b>Received chemotherapy, n(%)</b>        |             |            |             |
| No                                        | 808 (95.4%) | 93 (76.9%) | 191 (78.9%) |
| Yes                                       | 36 (4.3%)   | 27 (22.3%) | 46 (19.0%)  |
| Missing                                   | 3 (0.4%)    | 1 (0.8%)   | 5 (2.1%)    |
| <b>Received radiation, n(%)</b>           |             |            |             |
| No                                        | 459 (54.2%) | 70 (57.9%) | 188 (77.7%) |
| Yes                                       | 364 (43.0%) | 51 (42.1%) | 39 (16.1%)  |
| Missing                                   | 24 (2.8%)   | 0 (0%)     | 15 (6.2%)   |
| <b>Depression, n (%)</b>                  |             |            |             |
| No                                        | 153 (18.1%) | 19 (15.7%) | 34 (14.0%)  |
| Yes                                       | 34 (4.0%)   | 7 (5.8%)   | 12 (5.0%)   |
| Missing                                   | 660 (77.9%) | 95 (78.5%) | 196 (81.0%) |
| <b>History of prior CVD, Yes, n(%)</b>    | 138 (16.3%) | 17 (14.0%) | 32 (13.2%)  |
| <b>History of diabetes, Yes, n(%)</b>     | 201 (23.7%) | 29 (24.0%) | 51 (21.1%)  |
| <b>History of dyslipidemia, Yes, n(%)</b> | 555 (65.5%) | 60 (49.6%) | 130 (53.7%) |
| <b>History of hypertension, Yes, n(%)</b> | 593 (70.0%) | 67 (55.4%) | 159 (65.7%) |

Abbreviations: AI = Aromatase Inhibitor, SD = Standard Deviation, BMI = Body Mass Index, AJCC = American Joint Committee on Cancer, COPS2 = Comorbidity Point Score Version 2, CVD = Cardiovascular Disease

Definition of BMI category: Underweight: BMI less than 18.5 kg/m<sup>2</sup>; Normal: BMI 18.5 to <25 kg/m<sup>2</sup>; Overweight: BMI 25.0 to <30 kg/m<sup>2</sup>; Obese: BMI 30 or higher kg/m<sup>2</sup>.

**Supplemental Table 3. Characteristics of study participants who developed major adverse cardiovascular events within 12 months after breast cancer diagnosis (n=1,096)**

|                                                                                | <b>Non-user<br/>(n=270)</b> | <b>AI<br/>(n=710)</b> | <b>Tamoxifen<br/>(n=116)</b> | <b>Overall<br/>(n=1,096)</b> |
|--------------------------------------------------------------------------------|-----------------------------|-----------------------|------------------------------|------------------------------|
| <b>Age at BC diagnosis, y, mean (SD)</b>                                       | 73.4 (11.4)                 | 68.1 (9.70)           | 68.2 (11.3)                  | 69.4 (10.5)                  |
| <b>Race/ethnicity, n (%)</b>                                                   |                             |                       |                              |                              |
| American Indian and Alaska Native                                              | 2 (0.7%)                    | 1 (0.1%)              | 2 (1.7%)                     | 5 (0.5%)                     |
| Asian                                                                          | 29 (10.7%)                  | 107 (15.1%)           | 16 (13.8%)                   | 152 (13.9%)                  |
| Black                                                                          | 16 (5.9%)                   | 50 (7.0%)             | 8 (6.9%)                     | 74 (6.8%)                    |
| Hispanic                                                                       | 29 (10.7%)                  | 79 (11.1%)            | 6 (5.2%)                     | 114 (10.4%)                  |
| Pacific Islander                                                               | 1 (0.4%)                    | 0 (0%)                | 0 (0%)                       | 1 (0.1%)                     |
| White                                                                          | 193 (71.5%)                 | 473 (66.6%)           | 84 (72.4%)                   | 750 (68.4%)                  |
| <b>Percent neighborhood education of college graduate or higher, Mean (SD)</b> |                             |                       |                              |                              |
| Mean (SD)                                                                      | 0.216<br>(0.119)            | 0.238<br>(0.117)      | 0.227<br>(0.120)             | 0.232<br>(0.118)             |
| Missing                                                                        | 45 (16.7%)                  | 62 (8.7%)             | 22 (19.0%)                   | 129 (11.8%)                  |
| <b>Neighborhood median household income, \$, Mean (SD)</b>                     |                             |                       |                              |                              |
| Mean (SD)                                                                      | 74,100<br>(34,900)          | 80,100<br>(35,500)    | 80,800<br>(34,500)           | 78,800<br>(35,300)           |
| Missing                                                                        | 45 (16.7%)                  | 62 (8.7%)             | 22 (19.0%)                   | 129 (11.8%)                  |
| <b>BMI category, n (%)</b>                                                     |                             |                       |                              |                              |
| Underweight                                                                    | 43 (15.9%)                  | 46 (6.5%)             | 19 (16.4%)                   | 108 (9.9%)                   |
| Normal                                                                         | 66 (24.4%)                  | 157 (22.1%)           | 30 (25.9%)                   | 253 (23.1%)                  |
| Overweight                                                                     | 74 (27.4%)                  | 235 (33.1%)           | 36 (31.0%)                   | 345 (31.5%)                  |
| Obese                                                                          | 82 (30.4%)                  | 271 (38.2%)           | 31 (26.7%)                   | 384 (35.0%)                  |
| Missing                                                                        | 5 (1.9%)                    | 1 (0.1%)              | 0 (0%)                       | 6 (0.5%)                     |
| <b>BMI, kg/m<sup>2</sup></b>                                                   |                             |                       |                              |                              |
| Mean (SD)                                                                      | 27.0 (7.04)                 | 28.8 (6.65)           | 26.3 (6.35)                  | 28.1 (6.79)                  |
| Missing                                                                        | 5 (1.9%)                    | 1 (0.1%)              | 0 (0%)                       | 6 (0.5%)                     |
| <b>Waist circumference, cm</b>                                                 |                             |                       |                              |                              |
| Mean (SD)                                                                      | 91.4 (20.5)                 | 97.4 (21.9)           | 93.6 (21.9)                  | 95.7 (21.5)                  |
| Missing                                                                        | 246 (91.1%)                 | 640 (90.1%)           | 108 (93.1%)                  | 994 (90.7%)                  |
| <b>History of smoking, n (%)</b>                                               |                             |                       |                              |                              |
| Never                                                                          | 70 (25.9%)                  | 120 (16.9%)           | 18 (15.5%)                   | 208 (19.0%)                  |
| Ever                                                                           | 70 (25.9%)                  | 138 (19.4%)           | 31 (26.7%)                   | 239 (21.8%)                  |
| Missing                                                                        | 130 (48.1%)                 | 452 (63.7%)           | 67 (57.8%)                   | 649 (59.2%)                  |
| <b>AJCC stage, n (%)</b>                                                       |                             |                       |                              |                              |
| Stage I                                                                        | 184 (68.1%)                 | 393 (55.4%)           | 80 (69.0%)                   | 657 (59.9%)                  |
| Stage II                                                                       | 69 (25.6%)                  | 240 (33.8%)           | 29 (25.0%)                   | 338 (30.8%)                  |
| Stage III                                                                      | 17 (6.3%)                   | 77 (10.8%)            | 7 (6.0%)                     | 101 (9.2%)                   |
| <b>AI type, n (%)</b>                                                          |                             |                       |                              |                              |
| Anastrozole                                                                    | -                           | 628 (92.1%)           | -                            | -                            |
| Letrozole                                                                      | -                           | 61 (8.9%)             | -                            | -                            |

|                                            |            |             |             |             |             |
|--------------------------------------------|------------|-------------|-------------|-------------|-------------|
|                                            | Exemestane | -           | 21 (3.1%)   | -           |             |
| <b>Received chemotherapy, Yes, n (%)</b>   |            |             |             |             |             |
|                                            | No         | 226 (83.7%) | 506 (71.3%) | 89 (76.7%)  | 821 (74.9%) |
|                                            | Yes        | 31 (11.5%)  | 179 (25.2%) | 26 (22.4%)  | 236 (21.5%) |
|                                            | Missing    | 13 (4.8%)   | 25 (3.5%)   | 1 (0.9%)    | 39 (3.6%)   |
| <b>Received radiation, Yes, n (%)</b>      |            |             |             |             |             |
|                                            | No         | 168 (62.2%) | 379 (53.4%) | 59 (50.9%)  | 606 (55.3%) |
|                                            | Yes        | 59 (21.9%)  | 276 (38.9%) | 38 (32.8%)  | 373 (34.0%) |
|                                            | Missing    | 43 (15.9%)  | 55 (7.7%)   | 19 (16.4%)  | 117 (10.7%) |
| <b>COPS2</b>                               |            |             |             |             |             |
|                                            | Mean (SD)  | 22.3 (24.4) | 19.7 (24.7) | 18.5 (22.7) | 20.2 (24.4) |
|                                            | Missing    | 43 (15.9%)  | 55 (7.7%)   | 19 (16.4%)  | 117 (10.7%) |
| <b>Depression, n (%)</b>                   |            |             |             |             |             |
|                                            | No         | 19 (7.0%)   | 59 (8.3%)   | 6 (5.2%)    | 84 (7.7%)   |
|                                            | Yes        | 4 (1.5%)    | 13 (1.8%)   | 3 (2.6%)    | 20 (1.8%)   |
|                                            | Missing    | 247 (91.5%) | 638 (89.9%) | 107 (92.2%) | 992 (90.5%) |
| <b>History of prior CVD, Yes, n (%)</b>    |            | 73 (27.0%)  | 170 (23.9%) | 21 (18.1%)  | 264 (24.1%) |
| <b>History of diabetes, Yes, n (%)</b>     |            | 65 (24.1%)  | 216 (30.4%) | 21 (18.1%)  | 302 (27.6%) |
| <b>History of dyslipidemia, Yes, n (%)</b> |            | 166 (61.5%) | 501 (70.6%) | 68 (58.6%)  | 735 (67.1%) |
| <b>History of hypertension, Yes, n (%)</b> |            | 194 (71.9%) | 550 (77.5%) | 78 (67.2%)  | 822 (75.0%) |

Abbreviations: AI = Aromatase Inhibitor, AJCC = American Joint Committee on Cancer, BMI = Body Mass Index, COPS2 = Comorbidity Point Score Version 2, CVD = Cardiovascular Disease, SD = Standard Deviation

Definition of BMI category: Underweight: BMI less than 18.5 kg/m<sup>2</sup>; Normal: BMI 18.5 to <25 kg/m<sup>2</sup>; Overweight: BMI 25.0 to <30 kg/m<sup>2</sup>; Obese: BMI 30 or higher kg/m<sup>2</sup>.

Note: endocrine therapy was defined at the landmark time, i.e., 12 months after breast cancer diagnosis.

**Supplemental Table 4. Associations of endocrine therapy with CVD and mortality outcomes, using tamoxifen group as the reference group**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD Outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Tamoxifen | 52            | 13                     | 822                 | Ref               |
|                        | Non-user  | 100           | 32                     | 1224                | 1.02 [0.72, 1.43] |
|                        | AI        | 395           | 87                     | 5528                | 0.87 [0.65, 1.17] |
| Stroke                 | Tamoxifen | 27            | 6                      | 829                 | Ref               |
|                        | Non-user  | 58            | 11                     | 1245                | 1.06 [0.67, 1.69] |
|                        | AI        | 221           | 19                     | 5596                | 1.09 [0.73, 1.63] |
| Heart Failure          | Tamoxifen | 62            | 8                      | 827                 | Ref               |
|                        | Non-user  | 138           | 41                     | 1215                | 1.11 [0.82, 1.51] |
|                        | AI        | 460           | 69                     | 5546                | 0.88 [0.68, 1.16] |
| MACE                   | Tamoxifen | 139           | 26                     | 809                 | Ref               |
|                        | Non-user  | 270           | 87                     | 1169                | 1.04 [0.84, 1.28] |
|                        | AI        | 980           | 166                    | 5449                | 0.87 [0.73, 1.04] |
| Mortality Outcomes     |           |               |                        |                     |                   |
| All Death              | Tamoxifen | 226           | 7                      | 828                 | Ref               |
|                        | Non-user  | 525           | 45                     | 1211                | 1.22 [1.05, 1.44] |
|                        | AI        | 1554          | 31                     | 5584                | 0.91 [0.79, 1.05] |
| CVD Death              | Tamoxifen | 62            | 2                      | 833                 | Ref               |
|                        | Non-user  | 137           | 11                     | 1245                | 1.03 [0.76, 1.40] |
|                        | AI        | 354           | 7                      | 5608                | 0.76 [0.57, 0.99] |
| Non-CVD Death          | Tamoxifen | 164           | 5                      | 830                 | Ref               |
|                        | Non-user  | 388           | 34                     | 1222                | 1.30 [1.08, 1.56] |
|                        | AI        | 1200          | 24                     | 5591                | 0.97 [0.82, 1.14] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 5. Associations of endocrine therapy with CVD and mortality outcomes using the naïve method**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Non-user  | 103           | 0                      | 949                 | Ref               |
|                        | AI        | 420           | 48                     | 5281                | 0.76 [0.60, 0.96] |
|                        | Tamoxifen | 46            | 2                      | 500                 | 1.07 [0.75, 1.52] |
| Stroke                 | Non-user  | 60            | 0                      | 949                 | Ref               |
|                        | AI        | 222           | 9                      | 5320                | 0.84 [0.62, 1.14] |
|                        | Tamoxifen | 21            | 0                      | 502                 | 0.85 [0.51, 1.40] |
| Heart Failure          | Non-user  | 143           | 0                      | 949                 | Ref               |
|                        | AI        | 485           | 41                     | 5288                | 0.69 [0.56, 0.85] |
|                        | Tamoxifen | 41            | 2                      | 500                 | 0.69 [0.49, 0.99] |
| MACE                   | Non-user  | 291           | 0                      | 949                 | Ref               |
|                        | AI        | 1026          | 91                     | 5238                | 0.69 [0.60, 0.80] |
|                        | Tamoxifen | 105           | 4                      | 498                 | 0.85 [0.67, 1.06] |
| Mortality outcomes     |           |               |                        |                     |                   |
| All Death              | Non-user  | 446           | 0                      | 949                 | Ref               |
|                        | AI        | 1496          | 0                      | 5329                | 0.73 [0.65, 0.81] |
|                        | Tamoxifen | 142           | 0                      | 502                 | 0.74 [0.61, 0.90] |
| CVD Death              | Non-user  | 131           | 0                      | 949                 | Ref               |
|                        | AI        | 353           | 0                      | 5329                | 0.66 [0.53, 0.82] |
|                        | Tamoxifen | 42            | 0                      | 502                 | 0.84 [0.59, 1.19] |
| Non-CVD Death          | Non-user  | 315           | 0                      | 949                 | Ref               |
|                        | AI        | 1143          | 0                      | 5329                | 0.75 [0.66, 0.86] |
|                        | Tamoxifen | 100           | 0                      | 502                 | 0.71 [0.57, 0.90] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events  
 HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The naïve method followed up with non-users of endocrine therapy from breast cancer diagnosis date, while the follow-up of users began at the first AI or tamoxifen prescription.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 6. Associations of endocrine therapy use at six months after breast cancer diagnosis with CVD and mortality outcomes among postmenopausal women with hormone receptor-positive early-stage breast cancer**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Non-user  | 211           | 28                     | 2981                | Ref               |
|                        | AI        | 359           | 44                     | 4189                | 0.97 [0.81, 1.18] |
|                        | Tamoxifen | 55            | 6                      | 676                 | 1.14 [0.83, 1.55] |
| Stroke                 | Non-user  | 109           | 12                     | 2997                | Ref               |
|                        | AI        | 192           | 9                      | 4224                | 0.96 [0.74, 1.23] |
|                        | Tamoxifen | 29            | 2                      | 680                 | 1.02 [0.67, 1.55] |
| Heart Failure          | Non-user  | 276           | 35                     | 2974                | Ref               |
|                        | AI        | 390           | 37                     | 4196                | 0.82 [0.69, 0.97] |
|                        | Tamoxifen | 54            | 5                      | 677                 | 0.83 [0.62, 1.12] |
| MACE                   | Non-user  | 563           | 75                     | 2934                | Ref               |
|                        | AI        | 850           | 86                     | 4147                | 0.87 [0.77, 0.98] |
|                        | Tamoxifen | 130           | 13                     | 669                 | 0.94 [0.77, 1.15] |
| Mortality outcomes     |           |               |                        |                     |                   |
| All Death              | Non-user  | 1001          | 27                     | 2982                | Ref               |
|                        | AI        | 1210          | 7                      | 4226                | 0.80 [0.73, 0.88] |
|                        | Tamoxifen | 190           | 2                      | 680                 | 0.82 [0.70, 0.96] |
| CVD Death              | Non-user  | 232           | 6                      | 3003                | Ref               |
|                        | AI        | 293           | 1                      | 4232                | 0.73 [0.61, 0.88] |
|                        | Tamoxifen | 52            | 1                      | 681                 | 0.87 [0.64, 1.18] |
| Non-CVD Death          | Non-user  | 769           | 21                     | 2988                | Ref               |
|                        | AI        | 917           | 6                      | 4227                | 0.83 [0.74, 0.92] |
|                        | Tamoxifen | 138           | 1                      | 681                 | 0.81 [0.67, 0.98] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 7. Associations of endocrine therapy use at 12 months after breast cancer diagnosis with CVD and mortality outcomes, excluding 242 participants with uncertain status of endocrine therapy use**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Non-user  | 89            | 28                     | 1041                | Ref               |
|                        | AI        | 395           | 87                     | 5528                | 0.87 [0.69, 1.11] |
|                        | Tamoxifen | 52            | 13                     | 822                 | 1.01 [0.71, 1.43] |
| Stroke                 | Non-user  | 49            | 6                      | 1063                | Ref               |
|                        | AI        | 221           | 19                     | 5596                | 1.10 [0.80, 1.52] |
|                        | Tamoxifen | 27            | 6                      | 829                 | 1.02 [0.63, 1.64] |
| Heart Failure          | Non-user  | 126           | 30                     | 1039                | Ref               |
|                        | AI        | 460           | 69                     | 5546                | 0.79 [0.64, 0.98] |
|                        | Tamoxifen | 62            | 8                      | 827                 | 0.90 [0.66, 1.22] |
| MACE                   | Non-user  | 234           | 62                     | 1007                | Ref               |
|                        | AI        | 980           | 166                    | 5449                | 0.88 [0.75, 1.02] |
|                        | Tamoxifen | 139           | 26                     | 809                 | 1.01 [0.81, 1.25] |
| Mortality outcomes     |           |               |                        |                     |                   |
| All Death              | Non-user  | 451           | 8                      | 1061                | Ref               |
|                        | AI        | 1554          | 31                     | 5584                | 0.77 [0.69, 0.86] |
|                        | Tamoxifen | 226           | 7                      | 828                 | 0.84 [0.72, 0.99] |
| CVD Death              | Non-user  | 112           | 1                      | 1068                | Ref               |
|                        | AI        | 354           | 7                      | 5608                | 0.81 [0.64, 1.01] |
|                        | Tamoxifen | 62            | 2                      | 833                 | 1.07 [0.78, 1.47] |
| Non-CVD Death          | Non-user  | 339           | 7                      | 1062                | Ref               |
|                        | AI        | 1200          | 24                     | 5591                | 0.75 [0.66, 0.86] |
|                        | Tamoxifen | 164           | 5                      | 830                 | 0.78 [0.64, 0.94] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 8. Associations of endocrine therapy use at 12 months after breast cancer diagnosis with CVD and mortality outcomes, excluding participants with <80% medication possession ratio**

| Outcome                | Group     | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|-----------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |           |               |                        |                     |                   |
| Ischemic Heart Disease | Non-user  | 100           | 32                     | 1224                | Ref               |
|                        | AI        | 333           | 76                     | 4822                | 0.84 [0.67, 1.06] |
|                        | Tamoxifen | 47            | 10                     | 713                 | 1.00 [0.70, 1.42] |
| Stroke                 | Non-user  | 58            | 11                     | 1245                | Ref               |
|                        | AI        | 183           | 17                     | 4881                | 1.00 [0.74, 1.37] |
|                        | Tamoxifen | 26            | 3                      | 720                 | 1.04 [0.65, 1.66] |
| Heart Failure          | Non-user  | 138           | 41                     | 1215                | Ref               |
|                        | AI        | 397           | 63                     | 4835                | 0.79 [0.64, 0.97] |
|                        | Tamoxifen | 55            | 6                      | 717                 | 0.89 [0.65, 1.22] |
| MACE                   | Non-user  | 270           | 87                     | 1169                | Ref               |
|                        | AI        | 832           | 147                    | 4751                | 0.82 [0.71, 0.95] |
|                        | Tamoxifen | 130           | 19                     | 704                 | 1.01 [0.82, 1.25] |
| Mortality outcomes     |           |               |                        |                     |                   |
| All Death              | Non-user  | 525           | 45                     | 1211                | Ref               |
|                        | AI        | 1301          | 31                     | 4867                | 0.73 [0.65, 0.81] |
|                        | Tamoxifen | 199           | 7                      | 716                 | 0.82 [0.70, 0.97] |
| CVD Death              | Non-user  | 137           | 11                     | 1245                | Ref               |
|                        | AI        | 308           | 7                      | 4891                | 0.74 [0.59, 0.91] |
|                        | Tamoxifen | 58            | 2                      | 721                 | 1.03 [0.75, 1.40] |
| Non-CVD Death          | Non-user  | 388           | 34                     | 1222                | Ref               |
|                        | AI        | 993           | 24                     | 4874                | 0.72 [0.64, 0.82] |
|                        | Tamoxifen | 141           | 5                      | 718                 | 0.76 [0.63, 0.93] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events  
HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

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## **Chapter 2: Duration of aromatase inhibitor use and risk of cardiovascular disease and mortality in postmenopausal breast cancer survivors**

### **Abstract**

**Purpose:** Aromatase inhibitors (AIs) are used treat hormone receptor-positive breast cancer in postmenopausal women and breast cancer guidelines recommend long-term AI use. However, limited evidence exists on the effect of long-term AI use on cardiovascular disease (CVD) risk. We examined the risk of cardiovascular disease and mortality associated with duration of AI use in postmenopausal women with early-stage hormone receptor-positive breast cancer.

**Methods:** A total of 5,853 postmenopausal women were included who were diagnosed with stage I-III hormone receptor-positive breast cancer from 2005 to 2013 and part of the Pathways Heart Study, a prospective cohort study in Kaiser Permanente Northern California (KPNC). Breast cancer treatment, CVD outcomes, mortality, and covariate data were obtained from KPNC electronic health records, pharmacy claims, and linkage to the KPNC mortality file. Cause-specific hazards models were used to account for competing risks and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of duration of AI use (short-term:  $>0$  and  $<2$  years; intermediate-term:  $\geq 2$  and  $<5$  years; long-term:  $\geq 5$  years) with CVD and mortality outcomes. CVD outcomes included ischemic heart disease, heart failure, stroke, and major adverse cardiovascular events (MACE). Mortality outcomes included all-cause mortality, CVD-related mortality, and non-CVD-related mortality. The landmark method was used to avoid immortal time bias, and the selected landmark was 6 years after breast cancer diagnosis because participants had to survive the first 6 years since breast cancer diagnosis to become long-term AI users. Likelihood ratio tests were performed to examine whether the association of duration of AI use with CVD and mortality outcomes varied in strata defined by obesity, depression, and history of CVD prior to breast cancer diagnosis.

Results: Over a median follow-up of 3 (interquartile range = 0.2 to 5.2) years for women who survived 6 years after breast cancer diagnosis, a lower risk of stroke was observed in intermediate-term AI users (HR = 0.60, 95% CI = 0.37 to 0.96) and long-term AI users (HR = 0.51, 95% CI = 0.30 to 0.85), than in short-term AI users. The longer duration of AI use was also associated with lower risk of all-cause mortality and non-CVD-related mortality. In addition, long-term AI users were at 37% lower risk of CVD-related mortality (HR = 0.63, 95% CI = 0.42 to 0.95) than short-term AI users. No significant differences were observed in risks of MACE, ischemic heart disease, and heart failure across the three groups. The association between long-term AI use and non-CVD-related mortality differed in women with versus without a history of CVD prior to breast cancer diagnosis ( $P$  for interaction = 0.01); long-term AI users without CVD history were at lower risk of non-CVD-related mortality (HR = 0.47, 95% CI = 0.37 to 0.60) than short-term AI users without CVD history, whereas no such association was observed in the subgroup with CVD history.

Conclusion: Longer duration of AI use was not associated with elevated CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer. Our findings suggest long-term AI use reduces all-cause mortality risk and may not increase CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer.

## Introduction

Over 4 million women with a history of breast cancer live in the United States, with approximately 310,720 new cases expected in 2024.<sup>1</sup> About 80 percent of breast cancer cases are hormone receptor-positive,<sup>2</sup> and estrogen can promote the growth and proliferation of these breast cancer cells. Although endogenous estrogen is detrimental to women with hormone receptor-positive breast cancer, it may protect cardiovascular health through direct and indirect effects such as promoting vasorelaxation of vascular endothelial cells and reducing oxidative stress.<sup>3-5</sup>

Aromatase inhibitors (AIs) are used to halt the production of endogenous estrogen and treat hormone receptor-positive breast cancer in postmenopausal women. AI use may increase cardiovascular disease (CVD) risk because it decreases levels of potentially cardioprotective endogenous estrogen. Previous studies have yielded conflicting results and have focused on CVD risk comparing AI use to another endocrine therapy drug, tamoxifen, or non-users of endocrine therapy.<sup>6-14</sup> The inconsistency of these results may stem from the heterogeneous characteristics of study populations, various definitions of endocrine therapy use and CVD outcomes, and different approaches in calculating person-time. AIs are usually prescribed for five years. However, patients may discontinue AI treatment early due to side effects and cost. Despite breast cancer guidelines and results from clinical trials emphasizing the importance of long-term AI use ( $\geq 5$  years) given its favorable clinical outcomes,<sup>15-18</sup> few studies have examined the duration of AI exposure when investigating AI-related cardiovascular disease risk. The association between duration of AI use and subsequent CVD risk needs to be examined as duration of use is an important therapeutic characteristic of breast cancer treatment.

Obesity is a well-established risk factor of breast cancer as well as CVD. It may lead to alterations in drug pharmacokinetics and pharmacodynamics and may have a negative effect on AI efficacy in postmenopausal breast cancer women,<sup>19-21</sup> suggesting a potential interaction between AI use and obesity. However, obesity is often analyzed as a confounder rather than an effect modifier when examining the

association between AI use and CVD risk. Similar to obesity, although depression is linked with both CVD risk and lower medication adherence,<sup>22-24</sup> no studies have examined depression as an effect modifier of the association between duration of AI use and CVD risk. In addition, it is crucial to consider prior history of CVD in the context of CVD prevention,<sup>25</sup> given that patients with established CVD are at increased risk of recurrent CVD events.

We previously found that ever use of AIs in postmenopausal women was not associated with elevated CVD risk compared with non-users of endocrine therapy in Chapter 1. However, duration of AI use may affect cardiovascular health and comorbidities (i.e., obesity, depression, and CVD history) may modify the association. Thus, we conducted a prospective cohort study in postmenopausal women with early-stage hormone receptor-positive breast cancer to examine the associations of duration of AI use with CVD risk and mortality and whether the associations were modified by selected comorbidities. We hypothesized that longer duration of AI use would be associated with elevated CVD risk but reduced all-cause and non-CVD-related mortality risk due to its demonstrated effect in reducing breast cancer mortality,<sup>26,27</sup> in postmenopausal women with early-stage hormone receptor-positive breast cancer.

## **Methods**

### *Study population*

The National Cancer Institute (NCI)-funded Pathways Heart Study (R01CA214057, MPIs: Kwan and Greenlee) uses Kaiser Permanente Northern California (KPNC) electronic health record (EHR) data to examine incident CVD and cardiometabolic risk factors in women who were diagnosed with breast cancer from November 2005 to March 2013. Stage I-IV breast cancer patients who were female aged 21 years or older without a history of any invasive cancer were included in the Pathways Heart Study. For this analysis, the inclusion criteria were (1) postmenopausal women with a first-ever diagnosis of stage I-III breast cancer; (2) women who were eligible for endocrine therapy (with estrogen or progesterone receptor positive breast cancer); and (3) women who had at least one pharmacy fill of an AI. We excluded: (1)

women with evidence of metastatic disease because advanced disease stage may lead to significant variability in treatment response and prognosis, potentially confounding the study results (n = 320);<sup>28,29</sup> (2) women with AI and/or tamoxifen prescriptions prior to their breast cancer diagnosis because the exposure of interest was breast cancer treatment rather than prevention (n = 2); (3) women who had ever been treated with tamoxifen within 6 years after breast cancer diagnosis to avoid the confounding effect of tamoxifen (n = 1,772). Figure 1 presents the consort diagram of study population.

### *Data collection and measures*

Covariate data were obtained from KPNC EHR, including age, race, socioeconomic characteristics (i.e., percent neighborhood education of college graduate or higher and neighborhood median household income), body mass index (BMI), waist circumference, smoking history, the Comorbidity Point Score Version 2 (COPS2), and the Center for Epidemiologic Studies Depression (CES-D) score at baseline, which was defined as the date of breast cancer diagnosis. COPS2 is a measure of comorbidity developed and used internally at KPNC.<sup>30</sup> It is calculated using diagnostic codes of inpatient and outpatient encounters occurring in the year before diagnosis.<sup>30</sup> The CES-D scale was developed for epidemiology studies of depression and has been widely used and was administered to women enrolled in the main Pathways Study.<sup>31,32</sup> A CES-D score of 16 points or more was considered as having depression.<sup>31</sup> Overweight/obese was defined as a BMI greater than or equal to 25.0 kg/m<sup>2</sup>, and central obesity was defined as a waist circumference greater than or equal to the median value (96.8 cm) for the population. Data on waist circumference were only available in women who enrolled in the main Pathways Study.<sup>32</sup> Using clinically meaningful cutoff point of waist circumference would yield a very small sample size in the normal waist circumference group, and thus we used the median value of waist circumference to define central obesity. Baseline comorbidities including diabetes, dyslipidemia, and hypertension were defined using registry data, International Classification of Diseases (ICD) diagnostic codes, medication use, and/or laboratory results (details were described in Chapter 1).<sup>33</sup> Data on cancer characteristics, chemotherapy, radiation therapy, and endocrine therapy were obtained from the KPNC Cancer Registry

and supplemented by procedure, infusion, and outpatient pharmacy data sources. Total duration of AI use was calculated by summing the total days supplied starting from the earliest dispensing date after breast cancer diagnosis and ending at 6 years after breast cancer diagnosis (i.e., the landmark time). Since breast cancer guidelines recommend women with hormone receptor-positive breast cancer use endocrine therapy for at least 5 years and many discontinue the treatment early,<sup>15,18</sup> participants were classified into one of three groups: (1) short-term AI use ( $>0$  and  $<2$  years); (2) intermediate-term AI use ( $\geq 2$  and  $<5$  years); (3) long-term AI use ( $\geq 5$  years).

### *Outcome ascertainment*

The KPNC EHR was used to identify cardiovascular events through December 31, 2021 according to ICD diagnostic codes and Current Procedural Terminology codes from inpatient, ambulatory, and emergency department encounters and/or hospital discharge records (Supplemental Table 1). Data on death date and cause of death through December 31, 2021 were obtained from linkage to the KPNC mortality file, which contains data from the California State Department of Vital Statistics, US Social Security Administration, National Death Index, and KP membership and utilization data. The primary CVD outcome was a composite outcome of major adverse cardiovascular events (MACE), including ischemic heart disease (IHD), heart failure (HF), stroke, and CVD-related mortality. CVD-related mortality was defined as death due to IHD, stroke, HF, cardiomyopathy, arrhythmia, cardiac arrest, myocarditis/pericarditis, valvular disease, venous thromboembolism, and carotid disease. Secondary CVD outcomes included IHD, HF and stroke. Fatal CVD events were included in the corresponding CVD outcomes. Mortality outcomes included all-cause mortality, CVD-related mortality, and non-CVD-related mortality.

### *Statistical analysis*

The mean and standard deviation for continuous variables and frequency and percentage for categorical variables were used to summarize the baseline characteristics of study participants. To avoid immortal time bias, the landmark method was used to calculate person time.<sup>34</sup> The landmark method refers to the

analysis designating a time point occurring during the follow-up period (known as the landmark time) and analyzing only those subjects who have not developed outcome events by the landmark time. Since over 90% of users initiated endocrine therapy within one year after breast cancer diagnosis and long-term AI use was defined as  $\geq 5$  years, most participants had to survive the first 6 years since breast cancer diagnosis to become long-term AI users. Therefore, this study used 6 years after breast cancer diagnosis as the landmark time. Participants who were treated with tamoxifen or developed outcome events before the landmark time were excluded. The characteristics of women who were excluded due to the landmark method are presented in Supplemental Table 2. Follow up commenced 6 years after breast cancer diagnosis and ended on the date the outcome event occurred, health plan disenrollment, death, or end of study (December 31, 2021), whichever occurred first. Cause-specific hazards models were used to account for competing risks and to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of the association of duration of AI use with CVD and mortality outcomes. Complete cases analyses were performed. These models were adjusted for potential confounders including age at breast cancer diagnosis, race, percent neighborhood education of college graduate or higher, neighborhood median household income, BMI, history of ever smoking, American Joint Committee on Cancer (AJCC) stage, chemotherapy, and radiation, and additionally adjusted for precision variables including diabetes, dyslipidemia, hypertension, COPS2, and CVD history. Associations in subgroups defined by BMI and waist circumference, depression, and CVD history were examined by likelihood ratio tests. The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.<sup>35</sup> All analyses were performed using R (version 4.3.2, R development Core Team (2023)).<sup>36</sup>

### *Sensitivity analysis*

We conducted a sensitivity analysis using the naïve method rather than the landmark method to assess the magnitude of immortal time bias. In this analysis, the start dates of follow-time for the three groups of AI users were different: (1) for short-term AI users, it began on the date of first pharmacy fill of AI; (2) for

intermediate-term AI users, it began at the time when they had used AIs for two years; (3) for long-term AI users, it began at the time when they had used AIs for five years. The follow-up ended on the date the outcome event occurred, health plan disenrollment, death, or end of study (December 31, 2021), whichever occurred first. Intermediate-term and long-term AI users had to survive long enough without developing the outcome event to be included in this analysis. Therefore, the results using naïve methods are subject to immortal time bias.

## Results

### *Baseline characteristics*

A total of 5,853 postmenopausal women who were diagnosed with early-stage hormone receptor-positive breast cancer from 2005-2013 and used AIs within 6 years after diagnosis were included in this study. The average age of study participants was 66.2 (standard deviation = 8.9) years old and 70% were white (Table 1). Anastrozole was the most commonly used AI agent (n=5,582 (95.4%)). Compared to short-term AI users, intermediate-time AI users were more likely to be younger, have an obese BMI, receive chemotherapy, receive radiation, have a lower COPS2 (i.e., fewer comorbidities), and were less likely to have prevalent CVD and hypertension at baseline. Compared to short-term AI users, long-term AI users were more likely to be younger, live in neighborhood with higher median household income, receive chemotherapy, receive radiation, have a lower COPS2 (i.e., fewer comorbidities), and were less likely to have prevalent CVD and depression at baseline.

### *CVD risk and mortality risk*

Table 2 presents the results of the main association analysis. Over a median follow-up of 3.0 (interquartile range= 0.2 to 5.2) years (follow-up time started from 6 years after breast cancer diagnosis), intermediate-term and long-term AI users were less likely to develop stroke (HR = 0.60, 95% CI = 0.37 to 0.96 and HR = 0.51, 95% CI = 0.30 to 0.85, respectively) than short-term AI users. No significant differences were

observed in risks of MACE, IHD, and HF across the three groups, although all the point estimates of HRs were in the direction of inverse associations between longer duration of AI use and CVD risk.

Intermediate-term and long-term AI users had lower risk of all-cause mortality and non-CVD-related mortality as compared to short-term AI users. In addition, long-term AI users had a 37% lower risk of CVD-related mortality (HR = 0.63, 95% CI = 0.42 to 0.95), compared with short-term AI users.

#### *Interaction analysis: Obesity*

Tables 3 and 4 present the results of interaction analysis by overall obesity defined by BMI and central obesity defined by waist circumference. No significant interaction between duration of AI use and obesity was observed.

#### *Interaction analysis: Depression*

Table 5 presents the results of interaction analysis by depression. No significant interaction between duration of AI use and depression was observed.

#### *Interaction analysis: History of prior CVD*

Table 6 presents the results of interaction analysis by CVD history. Evidence of an interaction was found between duration of AI use and CVD history in relation to non-CVD-related mortality ( $P$  for interaction = 0.01); long-term AI users without CVD history were at decreased risk of non-CVD-related mortality (HR = 0.47, 95% CI = 0.37 to 0.60) compared with short-term AI users without CVD history, whereas no association was observed in the subgroup with CVD history.

#### *Sensitivity analysis*

Supplemental Table 3 presents the results of sensitivity analyses using the naïve method rather than the landmark method. Both intermediate-term AI use and long-term AI use were associated with lower risks

of MACE, IHD, stroke, HF, all-cause mortality, CVD-related mortality, and non-CVD-related mortality, compared with short-term AI use. The observed associations in the sensitivity analysis reflected the same direction as the main analysis. However, point estimates of HRs in sensitivity analysis were farther away from the null and the CIs were narrower due to substantial immortal time bias and more outcome events than the main analysis.

## **Discussion**

In this prospective cohort study of postmenopausal women who used AIs to treat early-stage hormone receptor-positive breast cancer, longer duration of AI use was associated with lower risks of stroke, all-cause mortality, CVD-related mortality, and non-CVD-related mortality. The risk of MACE, IHD, and HF was not elevated in the intermediate-term and long-term AI users compared with short-term AI users. The association between the duration of AI use and non-CVD-related mortality was modified by CVD history; long-term users without CVD history were at decreased risk of non-CVD-related mortality as compared to short-term users without CVD history, whereas no association was observed in the subgroup with CVD history. The results of our study need to be interpreted in relation to the selected landmark time; our study can only indicate CVD and mortality risk comparing women who use AIs for two to five years or five years and more to those who used AIs for less than two years within 6 years after breast cancer diagnosis. We confirmed our hypothesis that longer duration of AI use would reduce mortality risk. However, our findings were inconsistent with the hypothesis that longer duration of AI use would elevate CVD risk.

Our finding of 40-50% reduction in risk of stroke with longer duration of AI use needs to be interpreted with caution, as it was derived in a small sample size and was unexpected as our hypothesis was AIs might increase CVD risk. Although the biological mechanism of the observed association is unclear, one hypothesis is that AI users often take bisphosphonates to prevent bone fractures, and bisphosphonates may also be cardioprotective. However, evidence of cardioprotective effect of bisphosphonates is mixed.<sup>37-39</sup> Other possible explanations include confounding by unmeasured factors such as diet and

alcohol intake, residual confounding by inadequate adjustment, and bias by the healthy adherer effect, which arises when healthy behaviors are associated with both the adherence to treatment and the outcome of interest.<sup>40</sup> Although the direction of bias caused by unmeasured and residual confounding is unpredictable, when the healthy adherer effect exists, longer term AI use will appear more beneficial than shorter term AI use. However, it is also possible that our hypothesis was wrong, and AI use does not elevate CVD risk, which is consistent with the results of our Chapter 1.

We previously reported that breast cancer survivors who used AIs were at higher CVD risk than women without a history of breast cancer,<sup>41</sup> but the present study did not find elevated CVD risk associated with AI use. The results of our previous study may be biased due to confounding by indication; breast cancer and CVD have some common risk factors and breast cancer survivors who received endocrine therapy are sicker than women without a history of breast cancer, and thus AI use would appear to be harmful when comparing breast cancer survivors receiving AI treatment to women without a history of breast cancer.

To our knowledge, the present study was the first study to investigate CVD and mortality risk comparing long-term ( $\geq 5$  years) and intermediate-term (2-5 years) AI use to short-term (less than 2 years) AI use. Previous studies comparing short-term AI use to non-users of endocrine therapy regarding CVD risk had conflicting results.<sup>8,13</sup> Haque et al. conducted a retrospective cohort study to examine the association between duration of AI use and CVD risk in postmenopausal women with hormone receptor-positive breast cancer and without prior CVD.<sup>13</sup> They started follow-up at breast cancer diagnosis and defined duration of AI use by summing the total days supplied starting from the earliest dispensing date after breast cancer diagnosis and ending at one of the study end points, making the study subject to immortal time bias.<sup>13</sup> They reported that using AI for more than three years was associated with decreased risk of HF/cardiomyopathy (HR = 0.56, 95% CI = 0.38 to 0.83), while using AI for one year was associated with increased risks of HF/cardiomyopathy (HR = 1.29, 95% CI = 1.01 to 1.64) and stroke (HR = 1.41, 95% CI = 1.94 to 1.92), when compared with non-users of endocrine therapy.<sup>13</sup> They did not observe difference

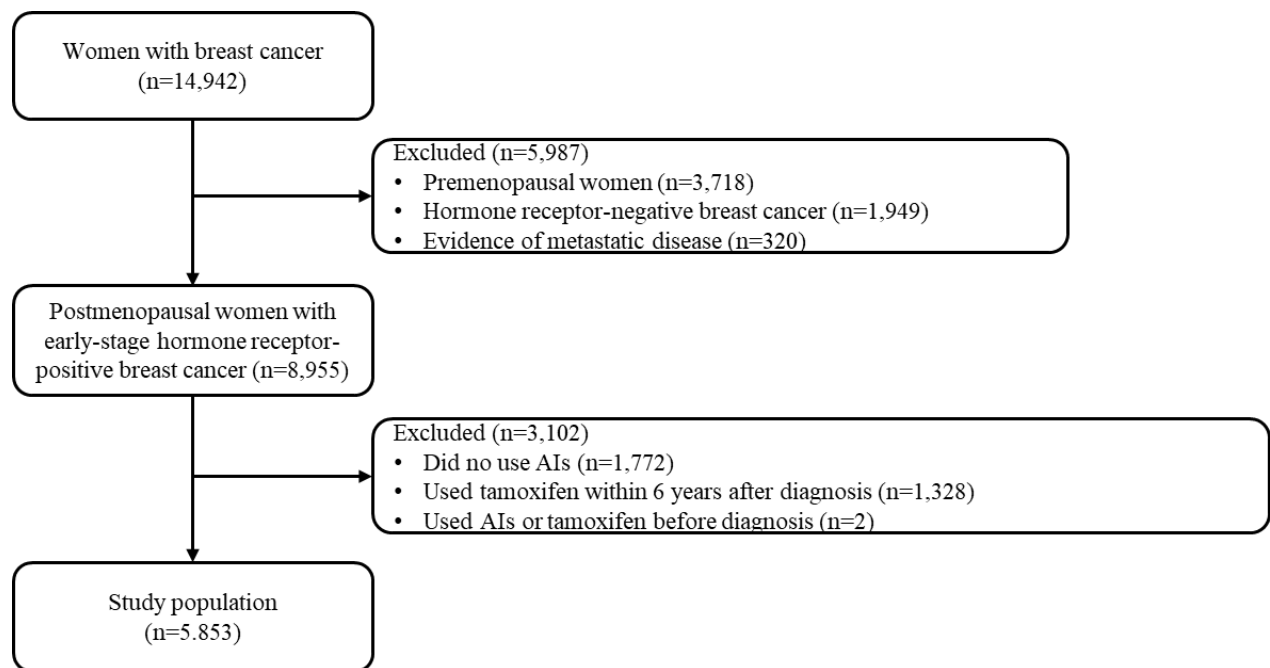
in risks of cardiac ischemia, stroke, and HF/cardiomyopathy comparing AI use for two to three years with non-use of endocrine therapy.<sup>13</sup> Another retrospective cohort study conducted by Sund et al. also examined the association between the duration of AI use and CVD risk.<sup>8</sup> They started follow-up at 6 months after breast cancer diagnosis and did not report the method to calculate duration of AI use.<sup>8</sup> Therefore, the study results were most likely affected by immortal time bias. They reported an elevated risk of acute IHD (HR = 2.03, 95% CI = 1.15 to 3.58) comparing AI use for more than four years with non-use of endocrine therapy or AI use less than one year in postmenopausal women with breast cancer.<sup>8</sup> No associations of the duration of AI use with HF/cardiomyopathy and stroke were found by Sund et al.<sup>8</sup>

Our study has several strengths. First, we followed study participants for a long period. The median follow-up time starting from breast cancer diagnosis was 9.0 (interquartile range = 6.2 to 11.2) years. Thus, we were able to estimate CVD and mortality risk related to long-term AI use ( $\geq 5$  years). Second, our study accounted for immortal time bias using the landmark method. Women who used AIs for five years or more had to survive long enough (i.e., 6 years after breast cancer diagnosis in our study) without developing the outcome events. When they are compared with women who only used AIs for two years, there is a time interval during which long-term AI users cannot develop the outcome of interest and thus the immortal time bias would be introduced if not utilizing appropriate statistical methods, as suggested by our sensitivity analyses. In addition, this study adopted short-term AI use rather than non-use of endocrine therapy as the reference group in regression models to avoid confounding by indication. We also excluded participants who were treated by tamoxifen to avoid bias by drug switching.

Our study also has several limitations. First, the study precision was limited because we used 6 years after breast cancer diagnosis as the landmark and excluded participants who developed the outcome before the landmark time. However, the selected landmark is necessary because a shorter landmark time will provide an incomplete capture of long-term AI use. Second, data on CES-D score and waist circumference were only available in women who enrolled in the main Pathways Study,<sup>32</sup> and thus the precision of HRs is

limited in strata defined by CES-D score and waist circumference. Third, our study did not consider different formulations of AIs. However, results from randomized clinical trials suggest no significant difference in CVD risk in the three AIs (i.e., anastrozole, letrozole and exemestane).<sup>42-46</sup> In addition, we enrolled women diagnosed with breast cancer from 2005 to 2013, and their utilization patterns of endocrine therapy may be different from what it is being used now. Moreover, another consideration is that our study may have reduced generalizability, because our study participants are all insured and have higher socioeconomic status compared with the general U.S. population. However, KPNC is generally representative of its catchment area, as KPNC provides care to over 30% of the population in counties with a physical service presence.

In postmenopausal women who used AIs to treat early-stage hormone receptor-positive breast cancer, we found evidence that longer duration of AI use assessed at 6 years after breast cancer diagnosis was associated with lower risk of stroke, all-cause mortality, CVD-related mortality, and non-CVD-related mortality. Our findings suggest AI use for two to five years or more than five years, assessed at 6 years after breast cancer diagnosis, reduces all-cause mortality risk and may not increase CVD risk in postmenopausal women with early-stage hormone receptor-positive breast cancer. Although our findings are observational and not definitive, these findings can help inform future hypotheses to test. Future studies with large sample size and addressing healthy adherer effect are needed to examine the association between long-term AI use and CVD risk.



**Figure 1: Consort diagram of study population**

**Table 1. Characteristics of study participants at breast cancer diagnosis by the duration of aromatase inhibitor use (n=5,853)**

|                                                                                | Short term (0-2 y)<br>(n = 1,159) | intermediate term (2-5 y)<br>(n=2,853) | Long term (≥5 y)<br>(n = 1,841) | Overall<br>(n = 5,853) |
|--------------------------------------------------------------------------------|-----------------------------------|----------------------------------------|---------------------------------|------------------------|
| <b>Age at diagnosis, y, mean (SD)</b>                                          | 68.4 (10.4)                       | 66.0 (8.8)                             | 65.1 (7.7)                      | 66.2 (8.9)             |
| <b>Race/ethnicity, n (%)</b>                                                   |                                   |                                        |                                 |                        |
| American Indian and Alaska Native                                              | 8 (0.7%)                          | 17 (0.6%)                              | 10 (0.5%)                       | 35 (0.6%)              |
| Asian                                                                          | 114 (9.8%)                        | 332 (11.6%)                            | 306 (16.6%)                     | 752 (12.8%)            |
| Black                                                                          | 83 (7.2%)                         | 168 (5.9%)                             | 91 (4.9%)                       | 342 (5.8%)             |
| Hispanic                                                                       | 127 (11.0%)                       | 323 (11.3%)                            | 155 (8.4%)                      | 605 (10.3%)            |
| Pacific Islander                                                               | 2 (0.2%)                          | 11 (0.4%)                              | 6 (0.3%)                        | 19 (0.3%)              |
| White                                                                          | 825 (71.2%)                       | 2,002 (70.2%)                          | 1,273 (69.1%)                   | 4,100 (70.0%)          |
| <b>Percent neighborhood education of college graduate or higher, Mean (SD)</b> |                                   |                                        |                                 |                        |
| Mean (SD)                                                                      | 0.229 (0.117)                     | 0.235 (0.115)                          | 0.243 (0.111)                   | 0.236 (0.114)          |
| Missing                                                                        | 12 (1.0%)                         | 32 (1.1%)                              | 14 (0.8%)                       | 58 (1.0%)              |
| <b>Neighborhood median household income, \$, Mean (SD)</b>                     |                                   |                                        |                                 |                        |
| Mean (SD)                                                                      | 78,600 (34,800)                   | 80,800 (33,600)                        | 85,100 (34,800)                 | 81,700 (34,300)        |
| Missing                                                                        | 12 (1.0%)                         | 32 (1.1%)                              | 14 (0.8%)                       | 58 (1.0%)              |
| <b>BMI category, n (%)</b>                                                     |                                   |                                        |                                 |                        |
| Underweight                                                                    | 8 (0.7%)                          | 26 (0.9%)                              | 11 (0.6%)                       | 45 (0.8%)              |
| Normal                                                                         | 341 (29.4%)                       | 732 (25.7%)                            | 514 (27.9%)                     | 1,587 (27.1%)          |
| Overweight                                                                     | 381 (32.9%)                       | 898 (31.5%)                            | 615 (33.4%)                     | 1,894 (32.4%)          |
| Obese                                                                          | 428 (36.9%)                       | 1,197 (42.0%)                          | 701 (38.1%)                     | 2,326 (39.7%)          |
| Missing                                                                        | 1 (0.1%)                          | 0 (0%)                                 | 0 (0%)                          | 1 (0.0%)               |
| <b>BMI, kg/m<sup>2</sup></b>                                                   |                                   |                                        |                                 |                        |
| Mean (SD)                                                                      | 28.9 (6.48)                       | 29.5 (6.50)                            | 29.1 (6.37)                     | 29.2 (6.46)            |
| Missing                                                                        | 1 (0.1%)                          | 0 (0%)                                 | 0 (0%)                          | 1 (0.0%)               |
| <b>Waist circumference, cm</b>                                                 |                                   |                                        |                                 |                        |
| Mean (SD)                                                                      | 97.9 (15.9)                       | 98.1 (17.0)                            | 97.1 (16.1)                     | 97.7 (16.5)            |
| Missing                                                                        | 868 (74.9%)                       | 2,051 (71.9%)                          | 1,348 (73.2%)                   | 4,267 (72.9%)          |
| <b>History of smoking, n (%)</b>                                               |                                   |                                        |                                 |                        |
| Never                                                                          | 559 (48.2%)                       | 1,455 (51.0%)                          | 1,032 (56.1%)                   | 3,046 (52.0%)          |
| Ever                                                                           | 497 (42.9%)                       | 1,201 (42.1%)                          | 691 (37.5%)                     | 2,389 (40.8%)          |
| Missing                                                                        | 103 (8.9%)                        | 197 (6.9%)                             | 118 (6.4%)                      | 418 (7.1%)             |
| <b>AJCC stage, n (%)</b>                                                       |                                   |                                        |                                 |                        |
| Stage I                                                                        | 694 (59.9%)                       | 1,621 (56.8%)                          | 1,064 (57.8%)                   | 3,379 (57.7%)          |
| Stage II                                                                       | 361 (31.1%)                       | 985 (34.5%)                            | 601 (32.6%)                     | 1,947 (33.3%)          |
| Stage III                                                                      | 104 (9.0%)                        | 247 (8.7%)                             | 176 (9.6%)                      | 527 (9.0%)             |
| <b>AI type, n (%)</b>                                                          |                                   |                                        |                                 |                        |
| Anastrozole                                                                    | 1,092 (94.2%)                     | 2,725 (95.5%)                          | 1,765 (95.9%)                   | 5,582 (95.4%)          |

|                                            |            |             |               |               |               |
|--------------------------------------------|------------|-------------|---------------|---------------|---------------|
|                                            | Letrozole  | 168 (14.5%) | 380 (13.3%)   | 251 (13.6%)   | 799 (13.7%)   |
|                                            | Exemestane | 93 (8.0%)   | 232 (8.1%)    | 120 (7.0%)    | 454 (7.8%)    |
| <b>Received chemotherapy, Yes, n (%)</b>   |            |             |               |               |               |
|                                            | No         | 926 (79.9%) | 1,970 (69.1%) | 1,172 (63.7%) | 4,068 (69.5%) |
|                                            | Yes        | 228 (19.7%) | 870 (30.5%)   | 662 (36.0%)   | 1,760 (30.1%) |
|                                            | Missing    | 5 (0.4%)    | 13 (0.5%)     | 7 (0.4%)      | 25 (0.4%)     |
| <b>Received radiation, Yes, n (%)</b>      |            |             |               |               |               |
|                                            | No         | 651 (56.2%) | 1,419 (49.7%) | 924 (50.2%)   | 2,994 (51.2%) |
|                                            | Yes        | 497 (42.9%) | 1,405 (49.2%) | 906 (49.2%)   | 2,808 (48.0%) |
|                                            | Missing    | 11 (0.9%)   | 29 (1.0%)     | 11 (0.6%)     | 51 (0.9%)     |
| <b>COPS2</b>                               |            |             |               |               |               |
|                                            | Mean (SD)  | 18.8 (22.8) | 13.9 (13.6)   | 13.0 (11.5)   | 14.6 (15.5)   |
|                                            | Missing    | 11 (0.9%)   | 29 (1.0%)     | 11 (0.6%)     | 51 (0.9%)     |
| <b>Depression, n (%)</b>                   |            |             |               |               |               |
|                                            | No         | 207 (17.9%) | 581 (20.4%)   | 406 (22.1%)   | 1,194 (20.4%) |
|                                            | Yes        | 78 (6.7%)   | 194 (6.8%)    | 82 (4.5%)     | 354 (6.0%)    |
|                                            | Missing    | 874 (75.4%) | 2,078 (72.8%) | 1,353 (73.5%) | 4,305 (73.6%) |
| <b>History of prior CVD, Yes, n (%)</b>    |            | 176 (15.2%) | 293 (10.3%)   | 165 (9.0%)    | 634 (10.8%)   |
| <b>History of diabetes, Yes, n (%)</b>     |            | 307 (26.5%) | 765 (26.8%)   | 482 (26.2%)   | 1,554 (26.6%) |
| <b>History of dyslipidemia, Yes, n (%)</b> |            | 755 (65.1%) | 1,974 (69.2%) | 1,308 (71.0%) | 4,037 (69.0%) |
| <b>History of hypertension, Yes, n (%)</b> |            | 794 (68.5%) | 1,995 (69.9%) | 1,343 (72.9%) | 4,132 (70.6%) |

Abbreviations: AI = Aromatase Inhibitor, AJCC = American Joint Committee on Cancer, BMI = Body Mass Index, COPS2 = Comorbidity Point Score Version 2, CVD = Cardiovascular Disease, SD = Standard Deviation

Definition of BMI category: Underweight: BMI less than 18.5 kg/m<sup>2</sup>; Normal: BMI 18.5 to <25 kg/m<sup>2</sup>; Overweight: BMI 25.0 to <30 kg/m<sup>2</sup>; Obese: BMI 30 or higher kg/m<sup>2</sup>.

Note: endocrine therapy was defined at the landmark time, i.e., 6 years after breast cancer diagnosis.

**Table 2. The associations of the duration of AI use with CVD and mortality outcomes using six years after breast cancer diagnosis as the landmark**

| Outcome                | Duration of AI use        | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|---------------------------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |                           |               |                        |                     |                   |
| Ischemic Heart Disease | Short-term (0-2 y)        | 22            | 68                     | 974                 | Ref               |
|                        | Intermediate-term (2-5 y) | 85            | 161                    | 2453                | 0.82 [0.51, 1.33] |
|                        | Long-term ( $\geq 5$ y)   | 59            | 73                     | 1629                | 0.68 [0.41, 1.13] |
| Stroke                 | Short-term (0-2 y)        | 25            | 41                     | 1001                | Ref               |
|                        | Intermediate-term (2-5 y) | 55            | 62                     | 2552                | 0.60 [0.37, 0.96] |
|                        | Long-term ( $\geq 5$ y)   | 35            | 14                     | 1688                | 0.51 [0.30, 0.85] |
| Heart Failure          | Short-term (0-2 y)        | 32            | 90                     | 952                 | Ref               |
|                        | Intermediate-term (2-5 y) | 110           | 146                    | 2468                | 0.87 [0.58, 1.30] |
|                        | Long-term ( $\geq 5$ y)   | 89            | 60                     | 1642                | 0.94 [0.62, 1.42] |
| MACE                   | Short-term (0-2 y)        | 67            | 193                    | 849                 | Ref               |
|                        | Intermediate-term (2-5 y) | 227           | 340                    | 2274                | 0.84 [0.63, 1.10] |
|                        | Long-term ( $\geq 5$ y)   | 162           | 133                    | 1569                | 0.75 [0.56, 1.01] |
| Mortality outcomes     |                           |               |                        |                     |                   |
| All Death              | Short-term (0-2 y)        | 177           | 307                    | 735                 | Ref               |
|                        | Intermediate-term (2-5 y) | 442           | 302                    | 2312                | 0.66 [0.55, 0.79] |
|                        | Long-term ( $\geq 5$ y)   | 273           | 16                     | 1686                | 0.56 [0.46, 0.68] |
| CVD Death              | Short-term (0-2 y)        | 40            | 60                     | 982                 | Ref               |
|                        | Intermediate-term (2-5 y) | 107           | 75                     | 2539                | 0.75 [0.52, 1.08] |
|                        | Long-term ( $\geq 5$ y)   | 65            | 6                      | 1696                | 0.63 [0.42, 0.95] |
| Non-CVD Death          | Short-term (0-2 y)        | 137           | 247                    | 795                 | Ref               |
|                        | Intermediate-term (2-5 y) | 335           | 227                    | 2387                | 0.63 [0.51, 0.77] |
|                        | Long-term ( $\geq 5$ y)   | 208           | 10                     | 1692                | 0.53 [0.42, 0.66] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at BC diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), ever smoking (yes, no), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 3. Effect modification of general obesity on the associations of duration of AI use with CVD and mortality outcomes using six years after breast cancer diagnosis as the landmark**

|                        |                           | Normal BMI    |                        |                     |                   | Overweight or Obese BMI |                        |                     |                   |                   |
|------------------------|---------------------------|---------------|------------------------|---------------------|-------------------|-------------------------|------------------------|---------------------|-------------------|-------------------|
| Outcome                | Duration of AI use        | No. of events | No. of excluded events | No. of participants | HR (95% CI)       | No. of events           | No. of excluded events | No. of participants | HR (95% CI)       | P for interaction |
| CVD outcomes           |                           |               |                        |                     |                   |                         |                        |                     |                   |                   |
| Ischemic Heart Disease | Short-term (0-2 y)        | 4             | 17                     | 292                 | Ref               | 18                      | 51                     | 682                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 11            | 35                     | 641                 | -                 | 74                      | 126                    | 1812                | -                 | -                 |
|                        | Long-term (≥5 y)          | 15            | 10                     | 469                 | -                 | 44                      | 63                     | 1159                | -                 | -                 |
| Stroke                 | Short-term (0-2 y)        | 12            | 10                     | 299                 | Ref               | 13                      | 31                     | 702                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 14            | 20                     | 656                 | 0.31 [0.14, 0.68] | 41                      | 42                     | 1896                | 0.81 [0.43, 1.53] | 0.11              |
|                        | Long-term (≥5 y)          | 14            | 3                      | 476                 | 0.38 [0.17, 0.86] | 21                      | 11                     | 1211                | 0.57 [0.28, 1.16] | 0.49              |
| Heart Failure          | Short-term (0-2 y)        | 4             | 23                     | 286                 | Ref               | 28                      | 67                     | 666                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 11            | 26                     | 650                 | -                 | 99                      | 120                    | 1818                | -                 | -                 |
|                        | Long-term (≥5 y)          | 21            | 11                     | 468                 | -                 | 68                      | 49                     | 1173                | -                 | -                 |
| MACE                   | Short-term (0-2 y)        | 19            | 48                     | 261                 | Ref               | 48                      | 145                    | 588                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 43            | 79                     | 597                 | 0.69 [0.40, 1.21] | 184                     | 261                    | 1677                | 0.86 [0.62, 1.19] | 0.50              |
|                        | Long-term (≥5 y)          | 47            | 24                     | 455                 | 0.87 [0.50, 1.52] | 115                     | 109                    | 1113                | 0.71 [0.50, 1.00] | 0.54              |

| Mortality outcomes |                           |     |     |     |                   |     |     |      |                   |      |
|--------------------|---------------------------|-----|-----|-----|-------------------|-----|-----|------|-------------------|------|
| All Death          | Short-term (0-2 y)        | 49  | 106 | 203 | Ref               | 128 | 201 | 532  | Ref               | Ref  |
|                    | Intermediate-term (2-5 y) | 118 | 88  | 588 | 0.79 [0.56, 1.11] | 324 | 214 | 1724 | 0.61 [0.49, 0.75] | 0.18 |
|                    | Long-term ( $\geq 5$ y)   | 77  | 8   | 471 | 0.63 [0.43, 0.91] | 196 | 8   | 1214 | 0.52 [0.42, 0.66] | 0.20 |
|                    |                           |     |     |     |                   |     |     |      |                   |      |
| CVD Death          | Short-term (0-2 y)        | 8   | 20  | 289 | Ref               | 32  | 40  | 693  | Ref               | Ref  |
|                    | Intermediate-term (2-5 y) | 25  | 26  | 650 | -                 | 82  | 49  | 1889 | -                 | -    |
|                    | Long-term ( $\geq 5$ y)   | 20  | 3   | 476 | -                 | 45  | 3   | 1219 | -                 | -    |
|                    |                           |     |     |     |                   |     |     |      |                   |      |
| Non-CVD Death      | Short-term (0-2 y)        | 41  | 86  | 223 | Ref               | 96  | 161 | 572  | Ref               | Ref  |
|                    | Intermediate-term (2-5 y) | 93  | 62  | 614 | 0.72 [0.49, 1.05] | 242 | 165 | 1773 | 0.59 [0.46, 0.75] | 0.33 |
|                    | Long-term ( $\geq 5$ y)   | 57  | 5   | 474 | 0.54 [0.36, 0.82] | 151 | 5   | 1217 | 0.52 [0.40, 0.67] | 0.61 |
|                    |                           |     |     |     |                   |     |     |      |                   |      |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), history of ever smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 4. Effect modification of central obesity on the associations of the duration of AI use with CVD and mortality outcomes using six years after breast cancer diagnosis as the landmark**

| Waist circumference ≤ 96.8 cm |                           |               |                        |                     |             | Waist circumference > 96.8 cm |                        |                     |             |                   |
|-------------------------------|---------------------------|---------------|------------------------|---------------------|-------------|-------------------------------|------------------------|---------------------|-------------|-------------------|
| Outcome                       | Duration of AI use        | No. of events | No. of excluded events | No. of participants | HR (95% CI) | No. of events                 | No. of excluded events | No. of participants | HR (95% CI) | P for interaction |
| CVD outcomes                  |                           |               |                        |                     |             |                               |                        |                     |             |                   |
| Ischemic Heart Disease        | Short-term (0-2 y)        | 3             | 4                      | 138                 | Ref         | 9                             | 14                     | 131                 | Ref         | Ref               |
|                               | Intermediate-term (2-5 y) | 8             | 23                     | 373                 | -           | 13                            | 29                     | 369                 | -           | -                 |
|                               | Long-term (≥5 y)          | 9             | 6                      | 240                 | -           | 6                             | 19                     | 222                 | -           | -                 |
| Stroke                        | Short-term (0-2 y)        | 3             | 4                      | 138                 | Ref         | 8                             | 4                      | 141                 | Ref         | Ref               |
|                               | Intermediate-term (2-5 y) | 6             | 8                      | 388                 | -           | 14                            | 4                      | 394                 | -           | -                 |
|                               | Long-term (≥5 y)          | 3             | 2                      | 244                 | -           | 3                             | 2                      | 239                 | -           | -                 |
| Heart Failure                 | Short-term (0-2 y)        | 4             | 8                      | 134                 | Ref         | 8                             | 18                     | 127                 | Ref         | Ref               |
|                               | Intermediate-term (2-5 y) | 12            | 16                     | 380                 | -           | 33                            | 20                     | 378                 | -           | -                 |
|                               | Long-term (≥5 y)          | 10            | 4                      | 242                 | -           | 11                            | 12                     | 229                 | -           | -                 |
| MACE                          | Short-term (0-2 y)        | 8             | 14                     | 128                 | Ref         | 15                            | 34                     | 111                 | Ref         | Ref               |
|                               | Intermediate-term (2-5 y) | 28            | 41                     | 355                 | -           | 45                            | 53                     | 345                 | -           | -                 |
|                               | Long-term (≥5 y)          | 21            | 11                     | 235                 | -           | 20                            | 29                     | 212                 | -           | -                 |

| Mortality outcomes |                           |    |    |     |                      |    |    |     |                      |      |
|--------------------|---------------------------|----|----|-----|----------------------|----|----|-----|----------------------|------|
| All Death          | Short-term (0-2 y)        | 20 | 27 | 115 | Ref                  | 28 | 36 | 109 | Ref                  | Ref  |
|                    | Intermediate-term (2-5 y) | 66 | 30 | 366 | 0.77<br>[0.45, 1.30] | 90 | 25 | 373 | 0.75<br>[0.48, 1.16] | 0.68 |
|                    | Long-term (≥5 y)          | 34 | 3  | 243 | 0.59<br>[0.33, 1.05] | 53 | 2  | 239 | 0.71<br>[0.44, 1.15] | 0.66 |
| CVD Death          | Short-term (0-2 y)        | 2  | 2  | 140 | Ref                  | 11 | 7  | 138 | Ref                  | Ref  |
|                    | Intermediate-term (2-5 y) | 14 | 6  | 390 | -                    | 23 | 9  | 389 | -                    | -    |
|                    | Long-term (≥5 y)          | 10 | 1  | 245 | -                    | 14 | 2  | 239 | -                    | -    |
| Non-CVD Death      | Short-term (0-2 y)        | 18 | 25 | 117 | Ref                  | 17 | 29 | 116 | Ref                  | Ref  |
|                    | Intermediate-term (2-5 y) | 52 | 24 | 372 | 0.72<br>[0.41, 1.27] | 67 | 16 | 382 | 0.84<br>[0.48, 1.46] | 0.74 |
|                    | Long-term (≥5 y)          | 24 | 2  | 244 | 0.50<br>[0.26, 0.95] | 39 | 0  | 241 | 0.78<br>[0.43, 1.42] | 0.21 |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 5. Effect modification of depression on the associations of the duration of AI use with CVD and mortality outcomes using six years after breast cancer diagnosis as the landmark**

|                        |                           | Depression    |                        |                     |             | No depression |                        |                     |             |                   |
|------------------------|---------------------------|---------------|------------------------|---------------------|-------------|---------------|------------------------|---------------------|-------------|-------------------|
| Outcome                | Duration of AI use        | No. of events | No. of excluded events | No. of participants | HR (95% CI) | No. of events | No. of excluded events | No. of participants | HR (95% CI) | P for interaction |
| CVD outcomes           |                           |               |                        |                     |             |               |                        |                     |             |                   |
| Ischemic Heart Disease | Short-term (0-2 y)        | 2             | 4                      | 74                  | Ref         | 10            | 14                     | 188                 | Ref         | Ref               |
|                        | Intermediate-term (2-5 y) | 3             | 15                     | 178                 | -           | 18            | 34                     | 540                 | -           | -                 |
|                        | Long-term (≥5 y)          | 4             | 5                      | 77                  | -           | 10            | 20                     | 380                 | -           | -                 |
| Stroke                 | Short-term (0-2 y)        | 3             | 0                      | 78                  | Ref         | 8             | 7                      | 195                 | Ref         | Ref               |
|                        | Intermediate-term (2-5 y) | 6             | 0                      | 193                 | -           | 12            | 11                     | 563                 | -           | -                 |
|                        | Long-term (≥5 y)          | 1             | 1                      | 81                  | -           | 5             | 3                      | 397                 | -           | -                 |
| Heart Failure          | Short-term (0-2 y)        | 2             | 7                      | 71                  | Ref         | 10            | 19                     | 183                 | Ref         | Ref               |
|                        | Intermediate-term (2-5 y) | 10            | 14                     | 179                 | -           | 32            | 24                     | 550                 | -           | -                 |
|                        | Long-term (≥5 y)          | 4             | 3                      | 79                  | -           | 19            | 13                     | 387                 | -           | -                 |
| MACE                   | Short-term (0-2 y)        | 6             | 11                     | 67                  | Ref         | 17            | 35                     | 167                 | Ref         | Ref               |
|                        | Intermediate-term (2-5 y) | 17            | 24                     | 169                 | -           | 51            | 67                     | 507                 | -           | -                 |
|                        | Long-term (≥5 y)          | 7             | 7                      | 75                  | -           | 34            | 33                     | 367                 | -           | -                 |

| <b>Mortality outcomes</b> |                           |    |    |     |                      |     |    |     |                      |      |
|---------------------------|---------------------------|----|----|-----|----------------------|-----|----|-----|----------------------|------|
| All Death                 | Short-term (0-2 y)        | 13 | 14 | 64  | Ref                  | 36  | 46 | 156 | Ref                  | Ref  |
|                           | Intermediate-term (2-5 y) | 39 | 18 | 175 | 0.84<br>[0.42, 1.69] | 112 | 37 | 537 | 0.72<br>[0.49, 1.06] | 0.36 |
|                           | Long-term (≥5 y)          | 14 | 1  | 81  | 0.61<br>[0.27, 1.42] | 72  | 4  | 396 | 0.64<br>[0.42, 0.97] | 0.48 |
| CVD Death                 | Short-term (0-2 y)        | 4  | 1  | 77  | Ref                  | 9   | 7  | 195 | Ref                  | Ref  |
|                           | Intermediate-term (2-5 y) | 7  | 3  | 190 | -                    | 26  | 12 | 562 | -                    | -    |
|                           | Long-term (≥5 y)          | 3  | 1  | 81  | -                    | 21  | 2  | 398 | -                    | -    |
| Non-CVD Death             | Short-term (0-2 y)        | 9  | 13 | 65  | Ref                  | 27  | 39 | 163 | Ref                  | Ref  |
|                           | Intermediate-term (2-5 y) | 32 | 15 | 178 | -                    | 86  | 25 | 549 | -                    | -    |
|                           | Long-term (≥5 y)          | 11 | 0  | 82  | -                    | 51  | 2  | 398 | -                    | -    |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart

Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Table 6. Effect modification of CVD history on the associations of the duration of AI use with CVD and mortality outcomes using six years after breast cancer diagnosis as the landmark**

|                        |                           | Had CVD history |                        |                     |                   | No CVD history |                        |                     |                   |                   |
|------------------------|---------------------------|-----------------|------------------------|---------------------|-------------------|----------------|------------------------|---------------------|-------------------|-------------------|
| Outcome                | Duration of AI use        | No. of events   | No. of excluded events | No. of participants | HR (95% CI)       | No. of events  | No. of excluded events | No. of participants | HR (95% CI)       | P for interaction |
| CVD outcomes           |                           |                 |                        |                     |                   |                |                        |                     |                   |                   |
| Ischemic Heart Disease | Short-term (0-2 y)        | 3               | 38                     | 121                 | Ref               | 19             | 30                     | 853                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 11              | 66                     | 199                 | -                 | 74             | 95                     | 2254                | -                 | -                 |
|                        | Long-term (≥5 y)          | 11              | 33                     | 120                 | -                 | 48             | 40                     | 1509                | -                 | -                 |
| Stroke                 | Short-term (0-2 y)        | 10              | 10                     | 149                 | Ref               | 15             | 31                     | 852                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 7               | 11                     | 254                 | -                 | 48             | 51                     | 2298                | -                 | -                 |
|                        | Long-term (≥5 y)          | 6               | 3                      | 150                 | -                 | 29             | 11                     | 1538                | -                 | -                 |
| Heart Failure          | Short-term (0-2 y)        | 8               | 45                     | 114                 | Ref               | 24             | 45                     | 838                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 23              | 60                     | 205                 | -                 | 87             | 86                     | 2263                | -                 | -                 |
|                        | Long-term (≥5 y)          | 20              | 24                     | 129                 | -                 | 69             | 36                     | 1513                | -                 | -                 |
| MACE                   | Short-term (0-2 y)        | 14              | 80                     | 79                  | Ref               | 53             | 113                    | 770                 | Ref               | Ref               |
|                        | Intermediate-term (2-5 y) | 28              | 117                    | 148                 | 0.51 [0.25, 1.04] | 199            | 223                    | 2126                | 0.87 [0.64, 1.18] | 0.49              |

|                           |                           |    |    |     |                         |     |     |      |                         |      |
|---------------------------|---------------------------|----|----|-----|-------------------------|-----|-----|------|-------------------------|------|
|                           | Long-term<br>(≥5 y)       | 27 | 51 | 102 | 0.61<br>[0.30,<br>1.25] | 135 | 82  | 1467 | 0.75<br>[0.55,<br>1.04] | 0.78 |
| <b>Mortality outcomes</b> |                           |    |    |     |                         |     |     |      |                         |      |
| All Death                 | Short-term<br>(0-2 y)     | 38 | 77 | 82  | Ref                     | 139 | 230 | 653  | Ref                     | Ref  |
|                           | Intermediate-term (2-5 y) | 78 | 59 | 206 | 0.78<br>[0.52,<br>1.17] | 364 | 243 | 2106 | 0.64<br>[0.52,<br>0.78] | 0.47 |
|                           | Long-term<br>(≥5 y)       | 55 | 6  | 147 | 0.73<br>[0.47,<br>1.14] | 218 | 10  | 1539 | 0.52<br>[0.42,<br>0.65] | 0.09 |
| CVD Death                 | Short-term<br>(0-2 y)     | 14 | 20 | 139 | Ref                     | 26  | 40  | 843  | Ref                     | Ref  |
|                           | Intermediate-term (2-5 y) | 29 | 18 | 247 | 0.84<br>[0.43,<br>1.62] | 78  | 57  | 2292 | 0.74<br>[0.47,<br>1.16] | 0.95 |
|                           | Long-term<br>(≥5 y)       | 12 | 2  | 151 | 0.39<br>[0.17,<br>0.89] | 53  | 4   | 1545 | 0.71<br>[0.44,<br>1.15] | 0.32 |
| Non-CVD Death             | Short-term<br>(0-2 y)     | 24 | 57 | 102 | Ref                     | 113 | 190 | 693  | Ref                     | Ref  |
|                           | Intermediate-term (2-5 y) | 49 | 41 | 224 | 0.72<br>[0.43,<br>1.20] | 286 | 186 | 2163 | 0.60<br>[0.48,<br>0.75] | 0.47 |
|                           | Long-term<br>(≥5 y)       | 43 | 4  | 149 | 0.90<br>[0.52,<br>1.53] | 165 | 6   | 1543 | 0.47<br>[0.37,<br>0.60] | 0.01 |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events

HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no), dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The effect modification analyses were only performed within subgroups which had at least 10 outcomes events per exposure group to obtain more accurate estimation of the regression coefficients.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

**Supplemental Table 1. Standard codes for the ascertainment of non-fatal and fatal major cardiovascular events in the Pathways Heart Study**

|                                                           | <b>Primary International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) Diagnosis or Procedure Codes</b> | <b>Primary International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Diagnosis or Procedure Codes</b>                                                                                                                                         | <b>Current Procedural Terminology (CPT4®) Codes for Medical Billing Services</b> |
|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| <b>Ischemic Heart Disease</b>                             |                                                                                                                                        |                                                                                                                                                                                                                                                                                 |                                                                                  |
| 1. Acute myocardial infarction                            | 410.X                                                                                                                                  | I21.01, I21.02, I21.3, I21.4, I21.09, I21.11, I21.19, I21.21, I21.29, I22.0, I22.1, I22.2, I22.8, I22.9                                                                                                                                                                         | Not applicable                                                                   |
| 2. Other acute & subacute forms of ischemic heart disease | 411.X                                                                                                                                  | I20.0, I24.0, I24.1, I24.8, I24.9, I25.720, I25.750, I25.760, I25.790                                                                                                                                                                                                           | Not applicable                                                                   |
| 3. Angina pectoris                                        | 413.X                                                                                                                                  | I20.1, I20.8, I20.9, I25.110, I25.111, I25.118, I25.119, I25.701, I25.708, I25.709, I25.711, I25.718, I25.719, I25.721, I25.728, I25.729, I25.730, I25.731, I25.738, I25.739, I25.751, I25.758, I25.759, I25.761, I25.768, I25.769, I25.700, I25.710, I25.791, I25.798, I25.799 | Not applicable                                                                   |
| 4. Other ischemic heart disease                           | 414<br>414.8<br>414.9                                                                                                                  | I25.10, I25.110, I25.5, I25.6, I25.701, I25.711, I25.720, I25.721, I25.728, I25.729, I25.731, I25.738, I25.739, I25.750, I25.751, I25.758, I25.759, I25.760, I25.761, I25.768, I25.769, I25.790, I25.791, I25.798, I25.799, I25.810, I25.811, I25.812, I25.89, I25.9            | Not applicable                                                                   |
| 5. Aortocoronary bypass status convert                    | V45.81                                                                                                                                 | Z95.1                                                                                                                                                                                                                                                                           | Not applicable                                                                   |
| 6. Percutaneous transluminal coronary angioplasty status  | V45.82                                                                                                                                 | Z95.5, Z98.61                                                                                                                                                                                                                                                                   | Not applicable                                                                   |
| 7. Coronary artery bypass surgery (CABG)                  | 36.1<br>36.11                                                                                                                          | 0210083, 0210088, 0210089, 021008C, 021008F, 021008W, 0210093, 0210098,                                                                                                                                                                                                         | 33510, 33511, 33512, 33513, 33514, 33515, 33516, 33517,                          |

|       |                                     |                             |
|-------|-------------------------------------|-----------------------------|
| 36.12 | 0210099, 021009C, 021009F, 021009W, | 33518, 33519, 33520, 33521, |
| 36.13 | 02100A3, 02100A8, 02100A9, 02100AC, | 33522, 33523, 33525, 33530, |
| 36.14 | 02100AF, 02100AW, 02100J3, 02100J8, | 33533, 33534, 33535, 33536  |
| 36.15 | 02100J9, 02100JC, 02100JF, 02100JW, |                             |
| 36.16 | 02100K3, 02100K8, 02100K9, 02100KC, |                             |
| 36.17 | 02100KF, 02100KW, 02100Z3, 02100Z8, |                             |
| 36.19 | 02100Z9, 02100ZC, 02100ZF, 0210483, |                             |
| 36.03 | 0210488, 0210489, 021048C, 021048F, |                             |
|       | 021048W, 0210493, 0210498, 0210499, |                             |
|       | 021049C, 021049F, 021049W, 02104A3, |                             |
|       | 02104A8, 02104A9, 02104AC, 02104AF, |                             |
|       | 02104AW, 02104J3, 02104J8, 02104J9, |                             |
|       | 02104JC, 02104JF, 02104JW, 02104K3, |                             |
|       | 02104K8, 02104K9, 02104KC, 02104KF, |                             |
|       | 02104KW, 02104Z3, 02104Z8, 02104Z9, |                             |
|       | 02104ZC, 02104ZF, 0211083, 0211088, |                             |
|       | 0211089, 021108C, 021108F, 021108W, |                             |
|       | 0211093, 0211098, 0211099, 021109C, |                             |
|       | 021109F, 021109W, 02110A3, 02110A8, |                             |
|       | 02110A9, 02110AC, 02110AF, 02110AW, |                             |
|       | 02110J3, 02110J8, 02110J9, 02110JC, |                             |
|       | 02110JF, 02110JW, 02110K3, 02110K8, |                             |
|       | 02110K9, 02110KC, 02110KF, 02110KW, |                             |
|       | 02110Z3, 02110Z8, 02110Z9, 02110ZC, |                             |
|       | 02110ZF, 0211483, 0211488, 0211489, |                             |
|       | 021148C, 021148F, 021148W, 0211493, |                             |
|       | 0211498, 0211499, 021149C, 021149F, |                             |
|       | 021149W, 02114A3, 02114A8, 02114A9, |                             |
|       | 02114AC, 02114AF, 02114AW, 02114J3, |                             |
|       | 02114J8, 02114J9, 02114JC, 02114JF, |                             |
|       | 02114JW, 02114K3, 02114K8, 02114K9, |                             |
|       | 02114KC, 02114KF, 02114KW, 02114Z3, |                             |
|       | 02114Z8, 02114Z9, 02114ZC, 02114ZF, |                             |
|       | 0212083, 0212088, 0212089, 021208C, |                             |
|       | 021208F, 021208W, 0212093, 0212098, |                             |
|       | 0212099, 021209C, 021209F, 021209W, |                             |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |  |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | 02120A3, 02120A8, 02120A9, 02120AC,<br>02120AF, 02120AW, 02120J3, 02120J8,<br>02120J9, 02120JC, 02120JF, 02120JW,<br>02120K3, 02120K8, 02120K9, 02120KC,<br>02120KF, 02120KW, 02120Z3, 02120Z8,<br>02120Z9, 02120ZC, 02120ZF, 0212483,<br>0212488, 0212489, 021248C, 021248F,<br>021248W, 0212493, 0212498, 0212499,<br>021249C, 021249F, 021249W, 02124A3,<br>02124A8, 02124A9, 02124AC, 02124AF,<br>02124AW, 02124J3, 02124J8, 02124J9,<br>02124JC, 02124JF, 02124JW, 02124K3,<br>02124K8, 02124K9, 02124KC, 02124KF,<br>02124KW, 02124Z3, 02124Z8, 02124Z9,<br>02124ZC, 02124ZF, 0213083, 0213088,<br>0213089, 021308C, 021308F, 021308W,<br>0213093, 0213098, 0213099, 021309C,<br>021309F, 021309W, 02130A3, 02130A8,<br>02130A9, 02130AC, 02130AF, 02130AW,<br>02130J3, 02130J8, 02130J9, 02130JC,<br>02130JF, 02130JW, 02130K3, 02130K8,<br>02130K9, 02130KC, 02130KF, 02130KW,<br>02130Z3, 02130Z8, 02130Z9, 02130ZC,<br>02130ZF, 0213483, 0213488, 0213489,<br>021348C, 021348F, 021348W, 0213493,<br>0213498, 0213499, 021349C, 021349F,<br>021349W, 02134A3, 02134A8, 02134A9,<br>02134AC, 02134AF, 02134AW, 02134J3,<br>02134J8, 02134J9, 02134JC, 02134JF,<br>02134JW, 02134K3, 02134K8, 02134K9,<br>02134KC, 02134KF, 02134KW, 02134Z3,<br>02134Z8, 02134Z9, 02134ZC, 02134ZF,<br>0270046, 0270056, 027005Z, 0270066,<br>027006Z, 0270076, 027007Z, 02700D6,<br>02700DZ, 02700E6, 02700EZ, 02700F6,<br>02700FZ, 02700G6, 02700GZ, 02700T6, |  |
|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

|                                                   |      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                |
|---------------------------------------------------|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                                   |      | 02700TZ, 02700Z6, 02700ZZ, 0271046, 027104Z, 0271056, 027105Z, 0271066, 027106Z, 0271076, 027107Z, 02710D6, 02710DZ, 02710E6, 02710EZ, 02710F6, 02710FZ, 02710G6, 02710GZ, 02710T6, 02710TZ, 02710Z6, 02710ZZ, 0272046, 027204Z, 0272056, 027205Z, 0272066, 027206Z, 0272076, 027207Z, 02720D6, 02720DZ, 02720E6, 02720EZ, 02720F6, 02720FZ, 02720G6, 02720GZ, 02720T6, 02720TZ, 02720Z6, 02720ZZ, 0273046, 027304Z, 0273056, 027305Z, 0273066, 027306Z, 0273076, 027307Z, 02730D6, 02730DZ, 02730E6, 02730EZ, 02730F6, 02730FZ, 02730G6, 02730GZ, 02730T6, 02730TZ, 02730Z6, 02730ZZ, 02C00Z6, 02C00ZZ, 02C10Z6, 02C10ZZ, 02C20Z6, 02C20ZZ, 02C30Z6, 02C30ZZ           |                |
| 8. Percutaneous transluminal coronary angioplasty | 0.66 | 0270376, 02703D6, 02703E6, 02703EZ, 02703F6, 02703FZ, 02703G6, 02703GZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 0270446, 0270456, 027045Z, 0270466, 027046Z, 0270476, 027047Z, 02704D6, 02704DZ, 02704E6, 02704EZ, 02704F6, 02704FZ, 02704G6, 02704GZ, 02704T6, 02704TZ, 02704Z6, 02704ZZ, 02713D6, 02713DZ, 02713E6, 02713EZ, 02713F6, 02713FZ, 02713G6, 02713GZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 0271446, 027144Z, 0271456, 027145Z, 0271466, 027146Z, 0271476, 027147Z, 02714D6, 02714DZ, 02714E6, 02714EZ, 02714F6, 02714FZ, 02714G6, 02714GZ, 02714T6, 02714TZ, 02714Z6, 02714ZZ, 0272346, 027235Z, 0272366, 0272376, 02723D6, 02723DZ, 02723E6, 02723EZ, 02723F6, | Not applicable |

|  |  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |  |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  |  | 02723FZ, 02723G6, 02723GZ, 02723T6,<br>02723TZ, 02723Z6, 02723ZZ, 0272446,<br>027244Z, 0272456, 027245Z, 0272466,<br>027246Z, 0272476, 027247Z, 02724D6,<br>02724DZ, 02724E6, 02724EZ, 02724F6,<br>02724FZ, 02724G6, 02724GZ, 02724T6,<br>02724TZ, 02724Z6, 02724ZZ, 0273356,<br>027335Z, 0273366, 02733D6, 02733DZ,<br>02733E6, 02733EZ, 02733F6, 02733FZ,<br>02733G6, 02733GZ, 02733T6, 02733TZ,<br>02733Z6, 02733ZZ, 0273446, 027344Z,<br>0273456, 027345Z, 0273466, 027346Z,<br>0273476, 027347Z, 02734D6, 02734DZ,<br>02734E6, 02734EZ, 02734F6, 02734FZ,<br>02734G6, 02734GZ, 02734T6, 02734TZ,<br>02734Z6, 02734ZZ |  |
|--|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|

|                                                                                            |                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                        |
|--------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| <p>9. Percutaneous coronary intervention (PCI) with or without intra-coronary stenting</p> | <p>36.01, 36.02, 36.05, 36.06, 36.07, 36.09</p> | <p>0270046, 027004Z, 0270056, 027005Z, 0270066, 027006Z, 0270076, 027007Z, 02700D6, 02700DZ, 02700E6, 02700EZ, 02700F6, 02700FZ, 02700G6, 02700GZ, 02700T6, 02700TZ, 0270346, 027034Z, 0270356, 027035Z, 0270366, 027036Z, 0270376, 027037Z, 02703D6, 02703DZ, 02703E6, 02703EZ, 02703F6, 02703FZ, 02703G6, 02703GZ, 02703T6, 02703TZ, 0270446, 027044Z, 0270456, 027045Z, 0270466, 027046Z, 0270476, 027047Z, 02704D6, 02704DZ, 02704E6, 02704EZ, 02704F6, 02704FZ, 02704G6, 02704GZ, 02704T6, 02704TZ, 0271046, 027104Z, 0271056, 027105Z, 0271066, 027106Z, 0271076, 027107Z, 02710D6, 02710DZ, 02710E6, 02710EZ, 02710F6, 02710FZ, 02710G6, 02710GZ, 02710T6, 02710TZ, 0271346, 027134Z, 0271356, 027135Z, 0271366, 027136Z, 0271376, 027137Z, 02713D6, 02713E6, 02713F6, 02713FZ, 02713G6, 02713GZ, 02713T6, 02713TZ, 0271446, 027144Z, 0271456, 027145Z, 0271466, 027146Z, 0271476, 027147Z, 02714D6, 02714DZ, 02714E6, 02714EZ, 02714F6, 02714FZ, 02714G6, 02714GZ, 02714T6, 02714TZ, 0272046, 027204Z, 0272056, 027205Z, 0272066, 027206Z, 0272076, 027207Z, 02720D6, 02720DZ, 02720E6, 02720EZ, 02720F6, 02720FZ, 02720G6, 02720GZ, 02720T6, 02720TZ, 0272346, 027234Z, 0272356, 027235Z, 0272366, 027236Z, 0272376, 027237Z, 02723D6, 02723DZ, 02723E6, 02723EZ, 02723FZ, 02723G6, 02723GZ, 02723T6, 02723TZ, 0272446, 027244Z, 0272456,</p> | <p>92973, 92980, 92981, 92982, 92984, 92995, 92996</p> |
|--------------------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|

|                                    |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |
|------------------------------------|------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                    |                                                | 027245Z, 0272466, 027246Z, 0272476, 027247Z, 02724D6, 02724DZ, 02724E6, 02724EZ, 02724F6, 02724FZ, 02724G6, 02724GZ, 02724T6, 02724TZ, 0273046, 027304Z, 0273056, 027305Z, 0273066, 027306Z, 0273076, 027307Z, 02730D6, 02730DZ, 02730E6, 02730EZ, 02730F6, 02730FZ, 02730G6, 02730GZ, 02730T6, 02730TZ, 0273346, 027334Z, 0273356, 027335Z, 0273366, 027336Z, 0273376, 027337Z, 02733D6, 02733E6, 02733EZ, 02733F6, 02733FZ, 02733G6, 02733GZ, 02733T6, 02733TZ, 0273446, 027344Z, 0273456, 027345Z, 0273466, 027346Z, 0273476, 027347Z, 02734D6, 02734DZ, 02734E6, 02734EZ, 02734F6, 02734FZ, 02734G6, 02734GZ, 02734T6, 02734TZ, 02C03Z6, 02C03ZZ, 02C04Z6, 02C04ZZ, 02C13Z6, 02C13ZZ, 02C14Z6, 02C14ZZ, 02C23Z6, 02C23ZZ, 02C24Z6, 02C24ZZ, 02C33Z6, 02C33ZZ, 02C34Z6, 02C34ZZ |                |
| <b>Stroke, including TIA</b>       |                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                |
| 1. Transient Ischemic Attack (TIA) | 435.X                                          | G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, I67.841, I67.848                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Not applicable |
| 2. Acute Ischemic stroke           | 433.01<br>433.11<br>433.21<br>433.31<br>433.81 | I63.00, I63.02, I63.6, I63.8, I63.09, I63.9, I63.10, I63.011, I63.012, I63.12, I63.013, I63.019, I63.19, I63.20, I63.22, I63.29, I63.30, I63.031, I63.032, I63.033, I63.039, I63.39, I63.40, I63.49, I63.50, I63.59, I63.111, I63.112, I63.113, I63.119,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Not applicable |

|                                  |                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                |
|----------------------------------|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                  | 433.91<br>434.01<br>434.11<br>434.91<br>436 | I63.131, I63.132, I63.133, I63.139,<br>I63.211, I63.212, I63.213, I63.219,<br>I63.231, I63.232, I63.233, I63.239,<br>I63.311, I63.312, I63.313, I63.319,<br>I63.321, I63.322, I63.323, I63.329,<br>I63.331, I63.332, I63.333, I63.339,<br>I63.341, I63.342, I63.343, I63.349,<br>I63.411, I63.412, I63.413, I63.419,<br>I63.421, I63.422, I63.423, I63.429,<br>I63.431, I63.432, I63.433, I63.439,<br>I63.441, I63.442, I63.443, I63.449,<br>I63.511, I63.512, I63.513, I63.519,<br>I63.521, I63.522, I63.523, I63.529,<br>I63.531, I63.532, I63.533, I63.539,<br>I63.541, I63.542, I63.543, I63.549, I67.89 |                |
| 3. Subarachnoid hemorrhage       | 430.X                                       | I60.00, I60.01, I60.02, I60.2, I60.4, I60.6,<br>I60.7, I60.8, I60.9, I60.10, I60.11, I60.12,<br>I60.30, I60.31, I60.32, I60.50, I60.51,<br>I60.52                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Not applicable |
| 4. Intracerebral hemorrhage      | 431.X                                       | I61.0, I61.1, I61.2, I61.3, I61.4, I61.5,<br>I61.6, I61.8, I61.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Not applicable |
| 5. Retinal vascular occlusion    | 362.3                                       | G45.3, H34.00, H34.01, H34.02, H34.03,<br>H34.9, H34.10, H34.11, H34.12, H34.13,<br>H34.211, H34.212, H34.213, H34.219,<br>H34.231, H34.232, H34.233, H34.239,<br>H34.821, H34.822, H34.823, H34.829,<br>H34.8110, H34.8111, H34.8112,<br>H34.8120, H34.8121, H34.8122,<br>H34.8130, H34.8131, H34.8132,<br>H34.8190, H34.8191, H34.8192,<br>H34.8310, H34.8311, H34.8312,<br>H34.8320, H34.8321, H34.8322,<br>H34.8330, H34.8331, H34.8332,<br>H34.8390, H34.8391, H34.8392                                                                                                                                 | Not applicable |
| 6. Other cerebrovascular disease | 437.X<br>438.X                              | G45.4, G46.3, G46.4, G46.5, G46.6,<br>G46.7, G46.8, I67.1, I67.2, I67.4, I67.5,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Not applicable |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |  |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|
|  | I67.6, I67.7, I67.9, I67.81, I67.82, I68.0, I68.2, I68.8, I69.00, I69.010, I69.10, I69.011, I69.012, I69.013, I69.014, I69.015, I69.018, I69.019, I69.020, I69.20, I69.021, I69.022, I69.023, I69.028, I69.30, I69.031, I69.032, I69.033, I69.034, I69.039, I69.041, I69.042, I69.043, I69.044, I69.049, I69.051, I69.052, I69.053, I69.054, I69.059, I69.061, I69.062, I69.063, I69.064, I69.065, I69.069, I69.80, I69.090, I69.90, I69.091, I69.092, I69.093, I69.098, I69.110, I69.111, I69.112, I69.113, I69.114, I69.115, I69.118, I69.119, I69.120, I69.121, I69.122, I69.123, I69.128, I69.131, I69.132, I69.133, I69.134, I69.139, I69.141, I69.142, I69.143, I69.144, I69.149, I69.151, I69.152, I69.153, I69.154, I69.159, I69.161, I69.162, I69.163, I69.164, I69.165, I69.169, I69.190, I69.191, I69.192, I69.193, I69.198, I69.210, I69.211, I69.212, I69.213, I69.214, I69.215, I69.218, I69.219, I69.220, I69.221, I69.222, I69.223, I69.228, I69.231, I69.232, I69.233, I69.234, I69.239, I69.241, I69.242, I69.243, I69.244, I69.249, I69.251, I69.252, I69.253, I69.254, I69.259, I69.261, I69.262, I69.263, I69.264, I69.265, I69.269, I69.290, I69.291, I69.292, I69.293, I69.298, I69.310, I69.311, I69.312, I69.313, I69.314, I69.315, I69.318, I69.319, I69.320, I69.321, I69.322, I69.323, I69.328, I69.331, I69.332, I69.333, I69.334, I69.339, I69.341, |  |
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|                                                    |                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
|                                                    |                                                                                                                                                                                                                       | I69.342, I69.343, I69.344, I69.349,<br>I69.351, I69.352, I69.353, I69.354,<br>I69.359, I69.361, I69.362, I69.363,<br>I69.364, I69.365, I69.369, I69.390,<br>I69.391, I69.392, I69.393, I69.398,<br>I69.810, I69.811, I69.812, I69.813,<br>I69.814, I69.815, I69.818, I69.819,<br>I69.820, I69.821, I69.822, I69.823,<br>I69.828, I69.831, I69.832, I69.833,<br>I69.834, I69.839, I69.841, I69.842,<br>I69.843, I69.844, I69.849, I69.851,<br>I69.852, I69.853, I69.854, I69.859,<br>I69.861, I69.862, I69.863, I69.864,<br>I69.865, I69.869, I69.890, I69.891,<br>I69.892, I69.893, I69.898, I69.910,<br>I69.911, I69.912, I69.913, I69.914,<br>I69.915, I69.918, I69.919, I69.920,<br>I69.921, I69.922, I69.923, I69.928,<br>I69.931, I69.932, I69.933, I69.934,<br>I69.939, I69.941, I69.942, I69.943,<br>I69.944, I69.949, I69.951, I69.952,<br>I69.953, I69.954, I69.959, I69.961,<br>I69.962, I69.963, I69.964, I69.965,<br>I69.969, I69.990, I69.991, I69.992,<br>I69.993, I69.998 |                |
| <b>Heart Failure, including<br/>Cardiomyopathy</b> |                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                |
| <b>1. Heart Failure</b>                            | 398.91, 402.01, 402.11, 402.91,<br>404.11, 404.13, 428.0, 428.1, 428.9<br><br>404.01, 404.03, 404.91, 404.93,<br>428.20, 428.21, 428.22, 428.23,<br>428.30, 428.31, 428.32, 428.33,<br>428.40, 428.41, 428.42, 428.43 | I09.81, I11.0, I13.0, I13.2, I50, I50.1,<br>I50.2, I50.20, I50.21, I50.22, I50.23, I50.3,<br>I50.30, I50.31, I50.32, I50.33, I50.4,<br>I50.40, I50.41, I50.42, I50.43,<br><br>I50.8, I50.81, I50.810, I50.811, I50.812,<br>I50.813, I50.814, I50.82, I50.83, I50.84,<br>I50.89, I50.9, I97.13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Not applicable |

|                                      |                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                |
|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>2. Cardiomyopathy</b>             | 425.2, 425.4, 425.5, 425.7, 425.8, 425.9                                                                                                                                                                                                                                                                                      | I42.0, I42.5, I42.6, I42.7, I42.8, I42.9, I43,                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Not applicable |
| <b>Other CVD Outcomes</b>            |                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                |
| <b>Arrhythmia</b>                    | 426.0, 426.11, 426.12, 426.13, 426.3, 426.4, 426.6, 426.7, 427.0, 427.3X, 427.4X, 427.6, 427.8X, 427.9                                                                                                                                                                                                                        | I44.0, I44.1, I44.2, I44.7, I45.0, I45.5, I45.6, I45.10, I45.19, I47.1, I48.0, I48.1, I48.2, I48.3, I48.4, I48.91, I48.92, I49.01, I49.1, I49.02, I49.2, I49.3, I49.5, I49.8, I49.9, I49.40, I49.49, R00.1                                                                                                                                                                                                                                                                                                                                                                                                                                   | Not applicable |
| <b>Venous thromboembolic disease</b> | 415.1<br>415.11<br>415.19<br>451.1<br>451.2<br>451.8, 451.81, 451.83, 451.84, 451.89<br>451.9<br>452<br>453<br>453.1<br>453.2<br>453.3<br>453.40, 453.41, 453.42<br>453.5, 453.51, 453.52<br>453.72, 453.73, 453.74, 453.75, 453.76, 453.77, 453.79<br>453.8, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89<br>453.9 | I26.01, I26.02, I26.09, I26.90, I26.92, I26.99, I80.3, I80.8, I80.9, I80.10, I80.11, I80.12, I80.13, I80.201, I80.202, I80.203, I80.209, I80.211, I80.212, I80.213, I80.219, I80.221, I80.222, I80.223, I80.229, I80.231, I80.232, I80.233, I80.239, I80.291, I80.292, I80.293, I80.299, I82.0, I82.1, I82.90, I82.91, I82.210, I82.220, I82.221, I82.290, I82.601, I82.602, I82.603, I82.609, I82.611, I82.612, I82.613, I82.619, I82.621, I82.622, I82.623, I82.629, I82.890, I82.A11, I82.A12, I82.A13, I82.A19, I82.B11, I82.B12, I82.B13, I82.B19, I82.C11, I82.C12, I82.C13, I82.C19, T80.0XXA, T81.72XA, T81.718A, T82.817A, T82.818A | Not applicable |
| <b>Cardiac arrest</b>                | 427.5                                                                                                                                                                                                                                                                                                                         | I46.2, I46.8, I46.9                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                |

|                                 |                                                                                           |                                                                                                                                                                               |                |
|---------------------------------|-------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| <b>Myocarditis/Pericarditis</b> | 422.0, 422.90, 422.91, 422.92,<br>422.93, 422.99, 429.0, 420.0,<br>420.90, 420.91, 420.99 | A18.84, I30.0, I30.1, I30.8, I30.9, I32,<br>I40.0, I40.1, I40.8, I40.9, I41, I51.4,<br>M32.12                                                                                 | Not applicable |
| <b>Valvular disease</b>         | 424.0, 424.1, 424.2, 424.3<br><br>424.90, 424.91, 424.99                                  | A18.84, I34.0, I34.1, I34.2, I34.8, I34.9,<br>I35.0, I35.1, I35.2, I35.8, I35.9, I36.0,<br>I36.1, I36.2, I36.8, I36.9, I37.0, I37.1,<br>I37.2, I37.8, I37.9, I38, I39, M32.11 | Not applicable |
| <b>Carotid disease</b>          | 412.X<br>414.X                                                                            | I25.2, I25.3, I25.41, I25.42, I25.82, I25.83,<br>I25.84                                                                                                                       | Not applicable |

**Supplemental Table 2. Characteristics of study participants who developed major adverse events within 6 years after breast cancer diagnosis (n=1,161)**

|                                                                                | Short term (0-2 y)<br>(n = 310) | intermediate term (2-5 y)<br>(n=579) | Long term (≥5 y)<br>(n = 272) | Overall<br>(n = 1,161) |
|--------------------------------------------------------------------------------|---------------------------------|--------------------------------------|-------------------------------|------------------------|
| <b>Age at BC diagnosis, y, mean (SD)</b>                                       | 72.5 (10.8)                     | 69.6 (9.37)                          | 67.0 (8.46)                   | 69.8 (9.76)            |
| <b>Race/ethnicity, n (%)</b>                                                   |                                 |                                      |                               |                        |
| American Indian and Alaska Native                                              | 0 (0%)                          | 3 (0.5%)                             | 1 (0.4%)                      | 4 (0.3%)               |
| Asian                                                                          | 27 (8.7%)                       | 56 (9.7%)                            | 47 (17.3%)                    | 130 (11.2%)            |
| Black                                                                          | 30 (9.7%)                       | 48 (8.3%)                            | 17 (6.3%)                     | 95 (8.2%)              |
| Hispanic                                                                       | 38 (12.3%)                      | 65 (11.2%)                           | 27 (9.9%)                     | 130 (11.2%)            |
| Pacific Islander                                                               | 0 (0%)                          | 1 (0.2%)                             | 0 (0%)                        | 1 (0.1%)               |
| White                                                                          | 215 (69.4%)                     | 406 (70.1%)                          | 180 (66.2%)                   | 801 (69.0%)            |
| <b>Percent neighborhood education of college graduate or higher, Mean (SD)</b> |                                 |                                      |                               |                        |
| Mean (SD)                                                                      | 0.222 (0.118)                   | 0.233 (0.118)                        | 0.234 (0.114)                 | 0.230 (0.117)          |
| Missing                                                                        | 12 (3.9%)                       | 32 (5.5%)                            | 14 (5.1%)                     | 58 (5.0%)              |
| <b>Neighborhood median household income, \$, Mean (SD)</b>                     |                                 |                                      |                               |                        |
| Mean (SD)                                                                      | 74,300 (34,900)                 | 78,400 (34,200)                      | 80,500 (32,700)               | 77,800 (34,100)        |
| Missing                                                                        | 12 (3.9%)                       | 32 (5.5%)                            | 14 (5.1%)                     | 58 (5.0%)              |
| <b>BMI category, n (%)</b>                                                     |                                 |                                      |                               |                        |
| Underweight                                                                    | 8 (2.6%)                        | 26 (4.5%)                            | 10 (3.7%)                     | 44 (3.8%)              |
| Normal                                                                         | 80 (25.8%)                      | 135 (23.3%)                          | 59 (21.7%)                    | 274 (23.6%)            |
| Overweight                                                                     | 101 (32.6%)                     | 171 (29.5%)                          | 93 (34.2%)                    | 365 (31.4%)            |
| Obese                                                                          | 120 (38.7%)                     | 247 (42.7%)                          | 110 (40.4%)                   | 477 (41.1%)            |
| Missing                                                                        | 1 (0.3%)                        | 0 (0%)                               | 0 (0%)                        | 1 (0.1%)               |
| <b>BMI, kg/m<sup>2</sup></b>                                                   |                                 |                                      |                               |                        |
| Mean (SD)                                                                      | 29.1 (6.65)                     | 29.3 (6.87)                          | 29.7 (6.93)                   | 29.3 (6.82)            |
| Missing                                                                        | 1 (0.3%)                        | 0 (0%)                               | 0 (0%)                        | 1 (0.1%)               |
| <b>Waist circumference, cm</b>                                                 |                                 |                                      |                               |                        |
| Mean (SD)                                                                      | 102 (16.7)                      | 98.7 (21.2)                          | 105 (22.3)                    | 101 (20.5)             |
| Missing                                                                        | 258 (83.2%)                     | 477 (82.4%)                          | 226 (83.1%)                   | 961 (82.8%)            |
| <b>History of smoking, n (%)</b>                                               |                                 |                                      |                               |                        |
| Never                                                                          | 101 (32.6%)                     | 179 (30.9%)                          | 84 (30.9%)                    | 364 (31.4%)            |
| Ever                                                                           | 106 (34.2%)                     | 203 (35.1%)                          | 70 (25.7%)                    | 379 (32.6%)            |
| Missing                                                                        | 103 (33.2%)                     | 197 (34.0%)                          | 118 (43.4%)                   | 418 (36.0%)            |
| <b>AJCC stage, n (%)</b>                                                       |                                 |                                      |                               |                        |
| Stage I                                                                        | 183 (59.0%)                     | 322 (55.6%)                          | 144 (52.9%)                   | 649 (55.9%)            |
| Stage II                                                                       | 104 (33.5%)                     | 208 (35.9%)                          | 90 (33.1%)                    | 402 (34.6%)            |
| Stage III                                                                      | 23 (7.4%)                       | 49 (8.5%)                            | 38 (14.0%)                    | 110 (9.5%)             |

|                                            |             |             |             |               |  |
|--------------------------------------------|-------------|-------------|-------------|---------------|--|
| <b>AI type, n (%)</b>                      |             |             |             |               |  |
| Anastrozole                                | 281 (90.6%) | 549 (94.8%) | 258 (94.9%) | 1,088 (93.7%) |  |
| Letrozole                                  | 40 (12.9%)  | 66 (11.4%)  | 31 (11.4%)  | 137 (11.8%)   |  |
| Exemestane                                 | 15 (4.8%)   | 36 (6.2%)   | 19 (7.0%)   | 70 (6.0%)     |  |
| <b>Received chemotherapy, Yes, n (%)</b>   |             |             |             |               |  |
| No                                         | 264 (85.2%) | 442 (76.3%) | 171 (62.9%) | 877 (75.5%)   |  |
| Yes                                        | 41 (13.2%)  | 124 (21.4%) | 94 (34.6%)  | 259 (22.3%)   |  |
| Missing                                    | 5 (1.6%)    | 13 (2.2%)   | 7 (2.6%)    | 25 (2.2%)     |  |
| <b>Received radiation, Yes, n (%)</b>      |             |             |             |               |  |
| No                                         | 192 (61.9%) | 302 (52.2%) | 141 (51.8%) | 635 (54.7%)   |  |
| Yes                                        | 107 (34.5%) | 248 (42.8%) | 120 (44.1%) | 475 (40.9%)   |  |
| Missing                                    | 11 (3.5%)   | 29 (5.0%)   | 11 (4.0%)   | 51 (4.4%)     |  |
| <b>COPS2</b>                               |             |             |             |               |  |
| Mean (SD)                                  | 28.4 (32.2) | 19.8 (21.3) | 17.9 (18.5) | 21.7 (24.5)   |  |
| Missing                                    | 11 (3.5%)   | 29 (5.0%)   | 11 (4.0%)   | 51 (4.4%)     |  |
| <b>Depression, n (%)</b>                   |             |             |             |               |  |
| No                                         | 40 (12.9%)  | 74 (12.8%)  | 39 (14.3%)  | 153 (13.2%)   |  |
| Yes                                        | 11 (3.5%)   | 25 (4.3%)   | 7 (2.6%)    | 43 (3.7%)     |  |
| Missing                                    | 259 (83.5%) | 480 (82.9%) | 226 (83.1%) | 965 (83.1%)   |  |
| <b>History of prior CVD, Yes, n (%)</b>    | 97 (31.3%)  | 145 (25.0%) | 63 (23.2%)  | 305 (26.3%)   |  |
| <b>History of diabetes, Yes, n (%)</b>     | 109 (35.2%) | 188 (32.5%) | 98 (36.0%)  | 395 (34.0%)   |  |
| <b>History of dyslipidemia, Yes, n (%)</b> | 224 (72.3%) | 431 (74.4%) | 217 (79.8%) | 872 (75.1%)   |  |
| <b>History of hypertension, Yes, n (%)</b> | 253 (81.6%) | 474 (81.9%) | 224 (82.4%) | 951 (81.9%)   |  |

Abbreviations: AI = Aromatase Inhibitor, AJCC = American Joint Committee on Cancer, BMI = Body Mass Index, COPS2 = Comorbidity Point Score Version 2, CVD = Cardiovascular Disease, SD = Standard Deviation  
Definition of BMI category: Underweight: BMI less than 18.5 kg/m<sup>2</sup>; Normal: BMI 18.5 to <25 kg/m<sup>2</sup>; Overweight: BMI 25.0 to <30 kg/m<sup>2</sup>; Obese: BMI 30 or higher kg/m<sup>2</sup>.

Note: endocrine therapy was defined at the landmark time, i.e., 6 years after BC diagnosis.

**Supplemental Table 3. Associations of the duration of AI use with CVD and mortality outcomes using the naïve method**

| Outcome                | Duration of AI use        | No. of events | No. of excluded events | No. of participants | HR (95% CI)       |
|------------------------|---------------------------|---------------|------------------------|---------------------|-------------------|
| CVD outcomes           |                           |               |                        |                     |                   |
| Ischemic Heart Disease | Short-term (0-2 y)        | 88            | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 139           | 74                     | 2275                | 0.48 [0.37, 0.63] |
|                        | Long-term ( $\geq 5$ y)   | 96            | 71                     | 1882                | 0.34 [0.25, 0.47] |
| Stroke                 | Short-term (0-2 y)        | 65            | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 98            | 11                     | 2338                | 0.46 [0.34, 0.64] |
|                        | Long-term ( $\geq 5$ y)   | 44            | 13                     | 1940                | 0.22 [0.15, 0.33] |
| Heart Failure          | Short-term (0-2 y)        | 120           | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 175           | 53                     | 2296                | 0.49 [0.38, 0.62] |
|                        | Long-term ( $\geq 5$ y)   | 130           | 48                     | 1905                | 0.39 [0.30, 0.50] |
| MACE                   | Short-term (0-2 y)        | 257           | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 385           | 125                    | 2224                | 0.48 [0.41, 0.57] |
|                        | Long-term ( $\geq 5$ y)   | 230           | 120                    | 1833                | 0.31 [0.25, 0.37] |
| Mortality outcomes     |                           |               |                        |                     |                   |
| All Death              | Short-term (0-2 y)        | 477           | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 683           | 0                      | 2349                | 0.46 [0.41, 0.52] |
|                        | Long-term ( $\geq 5$ y)   | 336           | 0                      | 1953                | 0.24 [0.21, 0.28] |
| CVD Death              | Short-term (0-2 y)        | 100           | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 172           | 0                      | 2349                | 0.57 [0.44, 0.74] |
|                        | Long-term ( $\geq 5$ y)   | 81            | 0                      | 1953                | 0.30 [0.22, 0.41] |
| Non-CVD Death          | Short-term (0-2 y)        | 377           | 0                      | 1027                | Ref               |
|                        | Intermediate-term (2-5 y) | 511           | 0                      | 2349                | 0.42 [0.37, 0.48] |
|                        | Long-term ( $\geq 5$ y)   | 255           | 0                      | 1953                | 0.22 [0.18, 0.26] |

Abbreviations: AI = Aromatase Inhibitor, CI = Confidence Interval, CVD = Cardiovascular Disease, IHD = Ischemic Heart Disease, HR = Hazard Ratio, MACE = Major Cardiovascular Adverse Events  
HRs adjusted for age at breast cancer diagnosis, race (white, non-white), percent neighborhood education of college graduate or higher (continuous), neighborhood median house income (continuous), body mass index (continuous), history of smoking (never, ever), American Joint Committee on Cancer stage (I, II, III), chemotherapy (yes, no), radiation (yes, no), diabetes (yes, no),

dyslipidemia (yes, no), hypertension (yes, no), Comorbidity Point Score Version 2 (continuous), CVD history (yes, no).

No. of excluded events refers to women who developed the outcome event before the landmark time.

The start dates of follow-time for the three groups of AI users using the naïve methods were as follows:

(1) for short-term AI users, it began on the date of first pharmacy fill of AI; (2) for intermediate-term AI users, it began at the time when they had used AIs for two years; (3) for long-term AI users, it began at the time when they had used AIs for five years. The follow-up ended on the date of outcome events occurred, health plan disenrollment, death, or end of study (December 31, 2021), whichever occurred first.

MACE: a composite outcome of IHD, stroke, heart failure, and CVD death.

CVD death: death due to IHD, stroke, heart failure, cardiomyopathy, arrhythmia, venous thromboembolic disease, cardiac arrest, myocarditis/pericarditis, valvular disease, and carotid disease.

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### **Chapter 3: The agreement between the self-reported Center for Epidemiologic Studies Depression scale for depressive symptoms and International Classification of Diseases-9 diagnosis codes for depression in breast cancer survivors**

#### **Abstract**

**Aim:** The Center for Epidemiologic Studies Depression (CES-D) scale is a validated and widely used measure of depressive symptoms in epidemiology observational research, while International Classification of Diseases (ICD) codes were designed to classify morbidity and mortality information for statistical purposes. Compared with using the CES-D questionnaire to measure depressive symptoms, using ICD codes is more efficient and cost effective. However, the validity of using ICD codes to identify patients with or without depression in observational epidemiology studies is unknown. We examined the agreement between the self-reported CES-D for depressive symptoms and ICD-9 codes for depression recorded in the electronic health record in a large cohort of breast cancer survivors.

**Methods:** This study leveraged data from the Pathways Study, a prospective cohort study of women with breast cancer from Kaiser Permanente Northern California (KPNC) between 2005 and 2013. The CES-D questionnaire was administered during the baseline interview, which typically occurred within two months post-breast cancer diagnosis. A CES-D score of 16 or higher was defined as having depressive symptoms. An ICD-9 code from any patient encounter reflecting any type of depression within one year after breast cancer diagnosis was defined as depression. We used the kappa statistic and the McNemar chi-square test to examine the agreement between depression defined by the CES-D scale and ICD-9 codes. Sensitivity and specificity of ICD-9 codes were calculated, using the CES-D scale as the reference standard.

Results: A total of 3,949 women with breast cancer were included in this study. The median CES-D score was 9 (interquartile range = 4 to 16). A total of 1,015 (25.7%) women had a CES-D score of 16 or more and were classified as depressed, while a total of 660 (16.7%) women were classified as depressed using ICD-9 codes. Depressive symptoms defined by the CES-D scale and depression defined by ICD-9 codes had slight agreement ( $\kappa = 0.16$ ). Their classification was significantly different ( $P < 0.0001$ ). Using the CES-D scale as the reference standard, the sensitivity and specificity of ICD-9 codes for depression were 42.3% and 77.6%, respectively.

Conclusions: The classification of depression by CES-D and ICD-9 codes was significantly different in breast cancer survivors. ICD-9 codes for depression misclassified depressed women as not depressed women and vice versa, suggesting that ICD-9 codes are not a valid measure of depression in epidemiology studies of breast cancer.

## Introduction

Depressive disorders are a common mental health concern and characterized by a persistent depressed mood or loss of pleasure or interest in activities.<sup>1</sup> Depression has been an important concern for cancer patients, because it complicates the treatment of both depression and cancer and may lead to treatment non-adherence, and thus poorer clinical outcomes.<sup>2</sup> Approximately 32% of breast cancer patients have depression worldwide,<sup>3</sup> highlighting the need to screen for depressive symptoms and study the burden caused by depression in breast cancer survivors.

The World Health Organization developed International Classification of Diseases (ICD) codes to classify morbidity and mortality information for statistical purposes, and the use of ICD codes has expanded to various applications, including reimbursement, administration, epidemiology, and health services research.<sup>4</sup> Medical coders assign ICD codes for diagnoses and procedures after reviewing all pertinent medical record information.<sup>4</sup> . Although the use of ICD codes to measure depression is efficient and cost effective, these data are not designed for epidemiology research purposes and may misclassify depression. Therefore, it is important to assess the validity of these codes in epidemiology studies.

The Center for Epidemiologic Studies Depression scale (CES-D) was developed for epidemiology studies of depression rather than clinical diagnosis of depression and has been widely used.<sup>5</sup> It is a survey of 20 questions and the range of scores is 0 to 60. A CES-D score of 16 points or more is considered as having depression. Although the CES-D scale is a valid measure of depressive symptoms in epidemiology studies,<sup>6,7</sup> it is labor intensive and time consuming due to the requirement for a survey.

In Chapter 1 and 2, we examined the association between endocrine therapy use and cardiovascular disease risk stratified by depression defined by the CES-D scale. However, only a small portion of participants completed the CES-D questionnaire, and thus our stratified analyses were underpowered. If the CES-D scale shows good agreement with ICD codes for depression, which are available for all study participants, we can use ICD codes to define depression and the stratified analysis by depression would

have better power in Chapter 1 and 2. Hence, this study aimed to examine the agreement between the ICD codes and CES-D scale for depression in breast cancer survivors to provide evidence on the validity of ICD codes for depression used for epidemiology studies in breast cancer survivors.

## **Methods**

### *Study population*

The Pathways Study is a prospective cohort study that enrolled women with recently diagnosed breast cancer from Kaiser Permanente Northern California (KPNC) between 2005 and 2013.<sup>8</sup> Procedures for recruitment of study participants for the Pathways study have been described in detail previously.<sup>8</sup>

Eligible women were diagnosed with primary invasive breast cancer, 21 years or older, KPNC members, and had no prior history of cancer other than non-melanoma skin cancer. For this analysis, we included Pathways participants who were diagnosed with breast cancer and completed the CES-D questionnaire at baseline.

### *Data collection and measures*

Demographical data were abstracted from electronic health records (EHR). Cancer characteristics were obtained from the KPNC Cancer Registry. The CES-D questionnaire was administered during the baseline interview, which typically occurred within two months post-breast cancer diagnosis and took place in participants' homes. A CES-D score of 16 or higher was defined as depression.<sup>5</sup> Claims data on ICD codes for depression were abstracted from the KPNC EHR, which contains ICD codes for all patient encounters, including inpatient, outpatient, emergency room, and virtual visits. Since women included in this study were diagnosed with breast cancer between 2005 and 2013 and ICD-10 codes were not being used at that time, women with an ICD-9 code for any depression within one year after breast cancer diagnosis were considered as having depression. The ICD-9 codes for depression are presented in Table 1.

### *Statistical analysis*

The kappa statistic was estimated to examine the agreement between depression defined by the CES-D scale and ICD-9 codes. Interpretation of the kappa statistic was as follows:  $\leq 0$  indicated no agreement, 0.01–0.20 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 indicated almost perfect agreement.<sup>9</sup> The McNemar chi-square test was used to examine whether the classification of depression by the CES-D scale and ICD-9 codes was statistically different. The sensitivity and specificity of ICD-9 codes were calculated, using the CES-D scale as the reference standard. All analyses were performed using R (version 4.3.2, R development Core Team (2023)).<sup>10</sup>

## Results

A total of 3,949 women with breast cancer were included in this study. Table 2 presents the characteristics of study participants. The mean (standard deviation) age of study participants was 59.6 (12.0) years. The race/ethnicity groups of study participants included: White (n = 2,641 (66.9%)), Asian (n = 509 (12.9%)), Hispanic (n = 426 (10.8%)), Black (n = 283 (7.2%)), American Indian and Alaska Native (n = 78 (2.0%)), and Pacific Islander (n = 12 (0.3%)).

In the 3,949 women with breast cancer, the median CES-D score was 9 (interquartile range = 4 to 16). A total of 1,015 (25.7%) women had a CES-D score of 16 or more and were classified as depressed, while a total of 660 (16.7%) women were classified as depressed using ICD-9 codes. Table 3 presents the 2x2 table of depression defined by the CES-D scale and ICD-9 codes. Depression defined by the CES-D scale and ICD-9 codes had slight agreement (kappa = 0.16). Their classification of depression was significantly different ( $P < 0.0001$ ). Using the CES-D scale as the reference standard, the sensitivity and specificity of ICD-9 codes for depression were 42.3% and 77.6%, respectively.

## Discussion

In this observational study, we found poor agreement between depressive symptoms measured by the CES-D scale and depression defined by ICD-9 codes. ICD-9 codes for depression misclassified depressed

women as not depressed women and vice versa, suggesting that ICD-9 codes are not a valid measure of depression in epidemiology studies of breast cancer. If we perform interaction analyses by depression defined by ICD-9 codes in Chapter 1 and 2, our results may be biased; we may observe depression defined by ICD-9 codes did not modify the association between endocrine therapy and cardiovascular disease risk if depression measured by the CES-D scale truly modifies the association mentioned above.

ICD codes are the most widely used classification of diseases.<sup>4</sup> These codes are routinely used by researchers for multiple purposes, such as public health surveillance, clinical research, and health policy planning. Nevertheless, ICD codes are not flawless; studies have reported that ICD codes are subject to errors due to poor communication between patients and clinicians, lost or misplaced medical documents, transcription and scanning errors, etc.<sup>4,11,12</sup> Furthermore, using ICD codes to ascertain depression may be even more challenging. Clinicians have difficulty in diagnosing depression in routine practice and primary care providers can only correctly identify half of true depression cases.<sup>13</sup> Even when depression is diagnosed, only one in three depressed individuals has it documented in medical notes,<sup>13</sup> suggesting the substantial false negative rate when using ICD codes to ascertain depression.

There are several diagnostic instruments for depression, such as Diagnostic Interview Schedule (DIS), Composite International Diagnostic Interview (CIDI), and Structured Clinical Interview for DSM (SCID).<sup>13</sup> Given the time and expense required to administer these interviews, many epidemiology studies use self-reported questionnaires such as the CES-D scale as substitutions to measure depression. The CES-D scale has been validated by previous studies;<sup>6,7</sup> Beekman et al. reported good criterion validity of the CES-D scale for major depression in older adults aged 55 to 85 years,<sup>6</sup> and Hann et al. reported good construct validity of the CES-D scale for depressive symptoms in breast cancer patients,<sup>7</sup>

To the best of our knowledge, this study is the first study to examine the agreement between ICD codes for depression and the CES-D scale in breast cancer survivors. Boscarino et al. examined the agreement

between ICD-9 codes for depression and Patient Health Questionnaire (PHQ)-8 in patients with chronic hepatitis C infection.<sup>14</sup> They reported poor agreement on depression between ICD-9 codes and PHQ-8; ICD-9 codes predicting PHQ-8 depression had a sensitivity ranging from 59 to 88% and a specificity ranging from 33 to 65%.<sup>14</sup>

The present study also has several limitations. First, ICD-9 codes for depression and the CES-D scale assessed depression at different dates and over different periods; ICD-9 codes covered the entire year following breast cancer diagnosis, while the CES-D questionnaire was administered at breast cancer diagnosis and only covered the one week prior to the interview. In addition, our study only examined the prevalence of depression that occurred within one year after breast cancer diagnosis. However, depression may change over the course of breast cancer diagnosis and treatment.<sup>15</sup>

In conclusion, the agreement between the CES-D scale and ICD-9 codes for depression was poor in breast cancer survivors. Researchers should be cautious about using ICD-9 codes to ascertain depression in epidemiology studies of breast cancer, even if it is convenient. Future studies should account for depression medications when developing algorithms to define depression using ICD codes.

**Table 1. International Classification of Diseases (ICD) codes for depression**

| Diagnosis                                                                                                | ICD-9 Code |
|----------------------------------------------------------------------------------------------------------|------------|
| Major depressive affective disorder single episode mild degree                                           | 296.21     |
| Major depressive affective disorder single episode moderate degree                                       | 296.22     |
| Major depressive affective disorder single episode severe degree without psychotic behavior              | 296.23     |
| Major depressive affective disorder single episode severe degree specified as with psychotic behavior    | 296.24     |
| Major depressive affective disorder single episode in partial or unspecified remission                   | 296.25     |
| Major depressive affective disorder single episode in full remission                                     | 296.26     |
| Major depressive affective disorder single episode unspecified degree                                    | 296.2      |
| Major depressive affective disorder recurrent episode mild degree                                        | 296.31     |
| Major depressive affective disorder recurrent episode moderate degree                                    | 296.32     |
| Major depressive affective disorder recurrent episode severe degree without psychotic behavior           | 296.33     |
| Major depressive affective disorder recurrent episode severe degree specified as with psychotic behavior | 296.34     |
| Major depressive affective disorder recurrent episode in partial or unspecified remission                | 296.35     |
| Major depressive affective disorder recurrent episode in full remission                                  | 296.36     |
| Major depressive disorder recurrent episode                                                              | 296.3      |
| Dysthymic disorder                                                                                       | 300.4      |
| Mood disorder in conditions classified elsewhere                                                         | 293.83     |
| Depressive disorder not elsewhere classified                                                             | 311        |

**Table 2. Characteristics of study participants (n = 3,949)**

| Characteristics                                              | Mean (SD) or N (%) |
|--------------------------------------------------------------|--------------------|
| Age at breast cancer diagnosis, Years                        | 59.6 (12.0)        |
| Year of breast cancer diagnosis                              |                    |
| 2005                                                         | 19 (0.5%)          |
| 2006                                                         | 675 (17.1%)        |
| 2007                                                         | 733 (18.6%)        |
| 2008                                                         | 710 (18.0%)        |
| 2009                                                         | 485 (12.3%)        |
| 2010                                                         | 431 (10.9%)        |
| 2011                                                         | 496 (12.6%)        |
| 2012                                                         | 357 (9.0%)         |
| 2013                                                         | 43 (1.1%)          |
| Race/ethnicity                                               |                    |
| American Indian and Alaska Native                            | 78 (2.0%)          |
| Asian                                                        | 509 (12.9%)        |
| Black                                                        | 283 (7.2%)         |
| Hispanic                                                     | 426 (10.8%)        |
| Pacific Islander                                             | 12 (0.3%)          |
| White                                                        | 2,641 (66.9%)      |
| Neighborhood household income, \$                            | 83,600 (35,000)    |
| Percent neighborhood education of college graduate or higher | 0.25 (0.11)        |
| AJCC stage                                                   |                    |
| Stage I                                                      | 2,154 (54.5%)      |
| Stage II                                                     | 1,361 (34.5%)      |
| Stage III                                                    | 378 (9.6%)         |
| Stage IV                                                     | 56 (1.4%)          |
| Hormonal receptor status                                     |                    |
| Negative                                                     | 630 (16.0%)        |
| Positive                                                     | 3,315 (83.9%)      |
| Missing                                                      | 4 (0.1%)           |
| Received breast cancer surgery                               |                    |
| No                                                           | 151 (3.8%)         |
| Yes                                                          | 3,798 (96.2%)      |
| Received chemotherapy                                        |                    |
| No                                                           | 2,098 (53.1%)      |
| Yes                                                          | 1,839 (46.6%)      |
| Missing                                                      | 12 (0.3%)          |
| Received radiation                                           |                    |
| No                                                           | 2,179 (55.2%)      |
| Yes                                                          | 1,729 (43.8%)      |

|                            |         |               |
|----------------------------|---------|---------------|
|                            | Missing | 41 (1.0%)     |
| Received endocrine therapy |         |               |
|                            | No      | 967 (24.5%)   |
|                            | Yes     | 2,954 (74.8%) |
|                            | Missing | 28 (0.7%)     |

Abbreviations: AJCC = American Joint Committee on Cancer, IQR = Interquartile Range, SD = Standard Deviation

**Table 3. The 2x2 table of depression defined by the CES-D score and ICD-9 codes**

|            |               | CES-D       |               | Sensitivity | Specificity | Kappa statistic | P value  |
|------------|---------------|-------------|---------------|-------------|-------------|-----------------|----------|
|            |               | Depression  | No Depression |             |             |                 |          |
| ICD-9 code | Depression    | 279 (7.1%)  | 381 (9.6%)    | -           | -           | -               | -        |
|            | No Depression | 736 (18.6%) | 2553 (64.6%)  | 42.3%       | 77.6%       | 0.16            | < 0.0001 |

Abbreviations: CES-D = Center for Epidemiologic Studies Depression scale, ICD = International Classification of Diseases

P value from the McNemar chi-square test examined whether the classification of depression was statistically different.

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