



# Association between HIV infection and outcomes of care among medicare enrollees with breast cancer

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## ABSTRACT

**Background:** To assess the interaction of breast cancer, HIV infection, Medicare disability status, cancer stage and its implications for outcomes, after accounting for competing risks among female, fee-for-service Medicare enrollees.

**Methods:** We used data from Surveillance, Epidemiology and End Results (SEER) -Medicare (2000–2013). From primary female breast cancer cases diagnosed between 2001 and 2011, we identified those with HIV infection. We used Generalized Linear Model for phase-specific incremental cost of HIV, Cox regression for association between HIV and all-cause mortality, and Fine and Gray competing risk models to assess hazard of breast cancer-specific mortality by HIV status. We also studied this association for subgroups of cancer stage and disability status.

**Findings:** Of 164,080 eligible cases of breast cancer, 176 had HIV infection. Compared to HIV-uninfected patients, HIV infected patients had 16% higher cost in initial phase, and 80% higher cost in interim stage of care, and at least two times higher mortality (all-cause and breast cancer-specific), after accounting for competing risk. Among disabled enrollees, HIV-infected patients had higher risk of all-cause and breast cancer-specific mortality, compared to HIV-uninfected patients.

**Interpretation:** Female fee-for-service Medicare enrollees with breast cancer experience higher initial and interim phase cost and worse survival in the presence of HIV. This association was also significant among disabled Medicare enrollees. Medicare is the single largest source of federal financing for HIV care. Burden on Medicare will grow exponentially due to higher proportion of disabled among HIV-infected enrollees, longer survival among HIV-infected persons, increased HIV incidence in older adults, and increased age related risk of breast cancer. Future research can identify the pathways via which HIV infection affects cost and mortality, and develop integrated strategies for effective management of concomitant breast cancer and HIV and inform survivorship guidelines.

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## 1. Introduction

Improved survival due to antiretroviral therapy means that persons with HIV infection are living longer and face higher prevalence of concurrent medical conditions such as cancer [1]. The introduction of highly active antiretroviral therapy (HAART) for treatment of HIV in 1996, has helped lower the incidence of AIDS-defining cancers. However, studies show that impaired immune function remains a risk factor for cancer despite effective treatments [2, 3]. Research on the association between HIV and risk of breast cancer incidence is inconclusive. Studies have reported either no

association between HIV-infection and risk of breast cancer [4–9] or reduced risk [10, 11].

There is some evidence regarding aggressive clinical course and poorer outcomes of breast cancer in the presence of HIV, including younger age at diagnosis, [9, 12, 13] late diagnosis of cancer [6, 7, 14], and poorer response to chemotherapy [8, 15, 16]. Research indicates that in breast cancer patients, mortality is higher for those with concurrent HIV infection [14, 17–20]. The impaired survival may be due to the immunosuppression resulting from the HIV infection or due to nature of the tumor and associated treatments. The issue of competing risk among persons with breast cancer and HIV-infection is important. Competing risk is present when one type of event either precludes the occurrence of or fundamentally alters the probability of occurrence of the event of interest. One must evaluate the

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## Research in context

### Evidence before this study

Impaired immune function continues to be a risk factor for cancer. However, association between HIV and risk of breast cancer incidence is inconclusive. Some evidence exists regarding aggressive clinical behavior and impaired outcomes of breast cancer in the presence of HIV.

### Added value of this study

Our study will assess the interaction of breast cancer, HIV infection, Medicare disability, cancer stage and its implications for outcomes, after accounting for competing risks among female, fee-for-service Medicare enrollees.

### Implications of all the available evidence

Female fee-for-service Medicare enrollees with breast cancer experience higher phase-specific cost and worse survival in the presence of HIV. This association was also significant among disabled Medicare enrollees. Increase in the proportion of disabled among HIV-infected Medicare enrollees, longer survival among HIV-infected persons, increased incidence of HIV in older adults, and increased age related risk of breast cancer will exert high burden on Medicare. Integrated strategies for effective management of concomitant breast cancer and HIV are needed to inform survivorship care in this growing cohort.

stage and its implications for outcomes of care. Thus, the objective of our population-based study is to assess the outcomes of breast cancer care, phase-specific cost and mortality, in the presence of HIV infection, after accounting for competing mortality risks, and socio-demographic and clinical characteristics among female fee-for-service Medicare enrollees.

## 2. Methods

### 2.1. Study population

Population-based retrospective cohort study of Surveillance, Epidemiology, and End Results (SEER)-Medicare data from National Cancer Institute (NCI) for the period between 2000 and 2013. This data links SEER registries and Medicare claims, and provides detailed information about Medicare fee-for-service enrollees with cancer who reside in the SEER regions. The SEER program collects data on cancer incidence, treatment, and mortality from seventeen SEER sites and encompasses 26% of the US population. Of the elderly (aged  $\geq 65$  years) cancer patients in SEER registries, 93% have been matched with Medicare enrollment records [29].

We identified cases of primary female breast cancer diagnosed between 2000 and 2011 among fee-for-service Medicare enrollees (Fig. 1). We excluded cases confirmed on autopsy only, those enrolled in healthcare maintenance organization or those without part A and part B Medicare insurance in the 12 months prior to date of diagnosis. We then identified patients who also had a diagnosis of HIV or AIDS (ICD-9 codes 42.XX, V57) ascertained from inpatient, physician, and outpatient claims. To be classified as a valid case of HIV or AIDS, the patient had to have at least two outpatient claims or one inpatient claim with the relevant ICD-9 codes [30].

### 2.2. Outcomes

Outcomes were phase-specific cost of care, and mortality (all-cause and breast cancer-specific). We defined cost as reimbursements from Medicare. The continuum of breast cancer care was separated into three phases of care: initial phase (12 month following breast cancer diagnosis), terminal phase (12 months prior to death) and interim phase (period between initial phase and interim phase). Mortality status and number of surviving months was used to determine distribution of cost to a particular phase. For deceased patients who survived 12 months or less, the entire time was assigned to terminal phase; for those surviving between 13 and 24 months, last 12 months were assigned to terminal phase, and remaining time was assigned to initial phase; finally, for those surviving more than 24 months, 12 months prior to death was terminal phase, 12 months following diagnosis was

mortality among HIV-infected breast cancer patients in the presence of risk of dying from competing risks.

Research indicates that concurrent comorbid conditions among persons living with HIV leads to higher health service use and cost [21–24]. A study assessed the expenditure of Medicare enrollees living with HIV in year 2010, and noted that the presence of comorbidities increased the expenditure. The percentage increase in median spending associated with cancer was 25% [25].

Medicare eligibility can be due to age (65+) or due to Social Security Disability Insurance (SSDI) resulting from disability in patients younger than 65 years. Compared to non-disabled persons younger than 65, disabled Medicare patients had higher rates of cancer-related mortality for same stage of breast cancer [26, 27], and colorectal cancer [26], and lower adjusted rates of breast conserving surgery and radiation therapy [27, 28].

However, currently we have little knowledge about the interaction of breast cancer, HIV infection, Medicare disability status, cancer

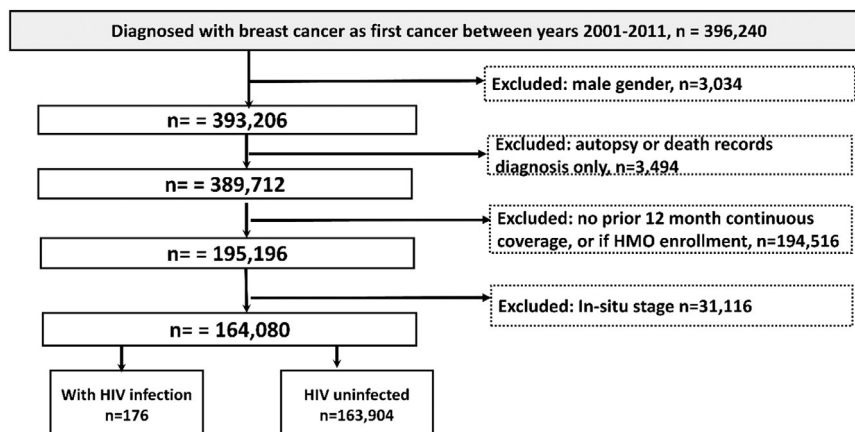


Fig. 1. Flow chart of cohort selection for cases diagnosed with primary female breast cancer between 2001 and 2011 among fee-for-service Medicare enrollees.

initial phase, and remaining time was interim phase. For patients who were alive at the study end (12/31/2013), there was no terminal phase. If survival (i.e., time since diagnosis to end of study) was 12 months or less, it was assigned to initial phase. For survival greater than 12 months, the first 12 months were initial phase and rest were assigned to interim phase. Several studies have followed similar method of attribution of phases of care [31–36]. Total costs for each phase included cost of care for the following services: inpatient, outpatient, physician/provider, durable medical equipment, home health agency and hospice. For mortality data, we used both SEER and Medicare files. Since SEER only reports month and year of death, we assigned 15 as the day of death to construct SEER date of death. For Medicare reported mortality, Medicare day, month, and year of death were used to create Medicare date of death. The patient was coded as deceased if SEER and/or Medicare reported him so. Breast cancer-specific mortality was obtained from SEER and for competing risk analysis patients were censored as of Dec 31, 2011 (at the time of the study, this was the most updated SEER data available). Medicare data were available for additional two years, and thus for all-cause mortality analysis, we censored patients as of Dec 31, 2013.

### 2.3. Covariates

Socio-demographic and clinical characteristics, age at diagnosis, race and ethnicity, marital status, census tract poverty indicator, Medicare eligibility criteria, and cancer stage, were obtained from the Patient Entitlement and Diagnosis File (PEDSF) of SEER. We used Medicare inpatient, outpatient and provider claims from the one-year before breast cancer diagnosis to develop Charlson co-morbidity index score. Surgical and radiation treatments for breast cancer were identified from SEER (PEDSF file) and from Medicare claims (eTable 1). Chemotherapy was ascertained from Medicare claims only [29].

### 2.4. Role of the funding source

The funding source did not have any role in the conduct of the study, writing of the manuscript, or the decision to submit it for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### 2.5. Data statement

The data used for the study cannot be shared as they were obtained from SEER-Medicare for this specific study.

## 3. Statistical analysis

We tested for differences in the demographic and clinical characteristics of breast cancer patients by HIV status, using *t*-tests and  $\chi^2$ -tests. Using the number of survival years in each phase, we determined average costs in each phase of care. We then compared these unadjusted costs (per surviving year) between HIV-infected and HIV-uninfected groups using *t*-tests. To study the phase-specific, incremental cost associated with HIV, we used generalized Linear Model (GLM) with log link function, with adjustment for socio-demographic and clinical covariates (age at diagnosis, race and ethnicity, marital status, census tract poverty indicator, Medicare eligibility criteria, comorbidity score, cancer stage, type of treatment, and year of breast cancer diagnosis). We modeled the association between HIV status and all-cause mortality using Cox regression model. The exposure variable of interest was HIV status, and we adjusted the model for socio-demographic and clinical covariates. Next, we analyzed the risk of breast cancer-specific mortality, in the presence of competing risk from other causes of death, using Fine and Gray models. We first accessed the cumulative incidence plot and then performed survival analysis with adjustment for socio-demographic

and clinical covariates. We repeated the analysis for two subgroups of cancer stage and two subgroups of Medicare eligibility criteria. Breast cancer treatment can affect outcomes, however, treatment assignments are not random. Therefore, using multinomial logistic regression, for each patient in our cohorts, we estimated the propensity of receiving a particular treatment based on age at diagnosis, race and ethnicity, marital status, census tract poverty indicator, Medicare eligibility criteria, comorbidity score, cancer stage, and year of breast cancer diagnosis. All analytical models were weighted by the inverse probability of propensity score. Analyses were performed using SAS Version 9.4 (SAS Institute, Cary, NC). This study uses de-identified, secondary data and was approved by the Institutional Review Board of University of Pennsylvania. Data use agreement was established with SEER-Medicare.

## 4. Results

Between 2001 and 2011, there were 396,240 cases of primary female breast cancer. After applying our selection criteria, we retained 164,080 cases (Fig. 1), and identified 176 women with a

**Table 1**

Characteristics of female, fee-for-service Medicare enrollees with primary breast cancer diagnosed between 2001 and 2011, by HIV status.

Characteristic	HIV-infected (N = 176) n (%)	HIV-uninfected (N = 163,904) n (%)	p-value
Age in years			
Mean $\pm$ SD	60.7 $\pm$ 12.8	75.4 $\pm$ 9.0	<0.0001
Race/Ethnicity			
White	67 (38.1)	134,135 (81.8)	<0.0001
African-American	87 (49.4)	153,78 (9.4)	
Hispanic/Others	22 (13.5)	14,391 (8.7)	
Marital status			
Married	46 (26.1)	65,378 (39.9)	0.0002
Census tract poverty indicator			
0%–5%	26 (14.8)	44,139 (26.9)	<0.0001
5% to <10%	25 (14.2)	44,767 (27.3)	
10% to <20%	59 (33.5)	45,339 (27.7)	
20% to <100%	66 (37.5)	29,659 (18.1)	
Reason for Medicare entitlement			
Age 65+	61 (34.7)	140,899 (85.9)	<0.0001
Disability or end stage renal disease (ESRD)	115 (65.3)	23,005 (14.0)	
Charlson comorbidity score			
<1	93 (52.8)	105,948 (64.6)	<0.0001
1–2	56 (31.8)	47,849 (29.2)	
>=3	27(15.4)	10,107 (6.2)	
Summary stage			
Local	101 (57.4)	107,180 (65.4)	0.0257
Regional/Distant	75 (42.6)	56,724 (34.6)	
Treatment			
Surgery alone	49 (27.4)	47,806 (29.2)	<0.0001
Surgery + radiation	47 (26.7)	45,883 (27.9)	
Surgery + radiation + chemo	40 (22.7)	16,119 (9.8)	
Surgery + Chemo	27 (15.3)	9452 (5.8)	
Radiation alone/chemo	– <sup>a</sup>	5345 (3.3)	
alone/radiation + chemo			
None	– <sup>a</sup>	39,299 (24.0)	
Year of breast cancer diagnosis			
2001–2003	49 (27.8)	45,967 (28.1)	0.9970
2004–2007	63 (35.8)	58,244 (35.5)	
2008–2011	64 (36.4)	59,693 (36.4)	
Vital status <sup>b</sup>			
Alive	92 (52.3)	95,700 (58.4)	0.1000
Deceased	84 (47.3)	68,204 (41.6)	
Breast cancer-specific death <sup>c</sup>	46 (54.8)	21,989 (32.2)	

<sup>a</sup> Numbers not reported due to small cell size.

<sup>b</sup> Vital status determined as of December 31, 2013 using Medicare claims and SEER data.

<sup>c</sup> Percentages of breast cancer-specific death were calculated as a proportion of total death.

diagnosis of HIV infection. As seen from Table 1, on average, HIV-infected breast cancer patients were younger compared with HIV-uninfected patients ( $60.7 \pm 12.8$  years vs.  $75.4 \pm 9.0$  years,  $p$  value  $<0.0001$ ,  $t$ -test). The HIV-infected group had higher proportion of African Americans (49% vs. 9%,  $p$  value  $<0.0001$ , chisq.), those unmarried (74% vs. 60%,  $p$  value = 0.0002, chisq.), with at least one comorbidity (48% vs. 35%,  $p$  value  $<0.0001$ , chisq), with regional or distant cancer stage (43% vs. 35%,  $p$  value = 0.0257, chisq) and those with SSDI disability status (65% vs. 14%,  $p$  value  $<0.0001$ , chisq.), compared to the HIV-uninfected patients. The treatment also differed between HIV-infected and HIV-uninfected groups. For HIV infected group, 93% of the women had surgery, either alone or with chemo and/or radiation. This proportion was 75% among HIV-uninfected women. The proportion of those receiving surgery alone, or surgery with radiation was only marginally different between the groups. However, the proportion of HIV-infected women who received surgery with chemo  $\pm$  radiation was higher that among HIV-uninfected women. Finally, only a small proportion of women from both group received radiation alone, chemo alone or radiation with chemo. About 24% of the HIV-uninfected group did not receive treatment, whereas this number was very small for the HIV-infected women. Within HIV-infected group, treatment differed by eligibility status. Lower proportion of SSDI disabled patients received surgery only, or surgery with radiation, and higher proportion received surgery with chemo, compared to the non-disabled patients (20% vs. 42%; 24% vs. 31%, and 21% vs.  $\leq 5\%$ , receptively). Among HIV-uninfected patients, lower proportion of disabled patients received surgery (alone or with chemo/radiation), and a higher proportion received no treatment, compared to non-disabled patients (32% vs. 79%, and 67% vs. 17%,  $p < .0001$ ; data not shown). All-cause mortality was 47% in the HIV-infected patients, compared to 42% in the HIV-uninfected patients. Among HIV-infected patients, 55% of the mortality was due to breast cancer, compared to 32% among HIV-uninfected patients (Table 1). Average number of surviving years was  $0.95 \pm 0.17$ ,  $5.05 \pm 3.29$  and  $0.92 \pm 0.16$  for HIV-infected group, and  $0.96 \pm 0.14$ ,  $4.96 \pm 3.13$  and  $0.90 \pm 0.23$  for HIV-uninfected group, for initial phase, interim phase and terminal phase, respectively.

#### 4.1. Cost of care

Unadjusted comparison of phase-specific cost of care for HIV-Infected and HIV-uninfected patients is presented in Table 2. The average cost (per surviving year) was higher for HIV-infected group for all phases of care, compared to the HIV-uninfected group ( $35,073 \pm 35,839$  vs.  $22,338 \pm 23,459$  for initial phase;  $18,846 \pm 25,983$  vs.  $9774 \pm 15,450$  for interim phase; and  $86,636 \pm 87,222$  vs.  $43,382 \pm 53,081$  for terminal

phase). Majority of the costs in all phases of care were attributed to inpatient, outpatient, and physician/provider costs. In Table 3, we present the results of GLM log-link model for phase-specific total cost of care. This inverse propensity score weighted analysis showed that the compared to HIV-uninfected patients, HIV-infected patients had 16% higher cost ( $p = .0019$ ) in the initial phase, and 80% higher cost ( $p < 0.0001$ ) in interim phase of care. In the terminal phase, the cost did not differ by HIV infection status. Similar results were observed for subgroup of patients with localized disease, and subgroup of disabled patients. On the other hand, the cost did not differ by HIV status for patients with regional/distant disease stage, and those who eligible for Medicare due to age, across any phase of care.

#### 4.2. Overall survival

The results of inverse propensity score weighted Cox regression showed that (Table 3), after adjusting for covariates, the hazard of all-cause mortality was higher for the HIV-infected patients, compared to the HIV-uninfected patients (HR=2.99, 95% CI=2.61, 3.43).

#### 4.3. Breast cancer-specific survival

In Fig. 2, we present the cumulative incidence function for breast cancer-specific mortality, in the presence of competing risk of death from other causes. It is observed that HIV-infected group had higher cumulative incidence rate of breast cancer-specific mortality, compared to HIV-uninfected patients (Gray's test  $p < .0001$ ).

The results of Fine and Gray competing risk model for breast cancer-specific survival (inverse propensity score weighted) is presented in Table 3. After adjusting for socio-demographic and clinical covariates, it was observed the hazard for breast cancer-specific mortality was higher for the HIV-infected patients, compared to HIV-uninfected patients (HR= 2.84, 95% CI=3.52).

#### 4.4. Cancer stage

For two subgroups of cancer stage - localized and regional/distant, we repeated the Cox regression analysis for all-cause mortality, and Fine and Gray competing risk analysis for breast cancer-specific mortality. As seen from Table 3, for localized and regional/distant subgroups, after adjusting for covariates and inverse propensity score weighting, the hazard of all-cause mortality was higher for the HIV-infected patients, compared to the HIV-uninfected patients (HR=3.55, 95% CI=2.87, 4.39 and HR=2.68, 95% CI=2.24, 3.20, respectively). Similarly, the hazard of breast cancer-specific mortality after accounting for competing risk was higher for the HIV-infected patients, compared to the HIV-uninfected patients.

**Table 2**  
Unadjusted phase-specific cost of care (per survival year) of female, fee-for-service Medicare enrollees with primary breast cancer diagnosed between 2001 and 2011, for HIV-infected and HIV-uninfected patients.

Cost (\$) Mean (std)	Initial phase			Interim phase			Terminal phase		
	HIV-infected n = 146	HIV-uninfected n = 133,993	P value	HIV-infected n = 131	HIV-uninfected n = 127,215	P value	HIV-infected n = 80	HIV-uninfected n = 64,395	P value
Total	35,073 (35,839)	22,338 (23,459)	<0.0001	18,846 (25,983)	9774 (15,450)	0.0001	86,636 (87,222)	43,382 (53,081)	<0.0001
Inpatient	9774 (26,337)	4378 (13,064)	0.0150	6443 (16,390)	3182 (9598)	0.0244	49,181 (73,731)	20,818 (42,485)	0.0009
Outpatient	11,013 (14,179)	6272 (8805)	<0.0001	4582 (7708)	1723 (4554)	<0.0001	11,651 (14,471)	3912 (8661)	<0.0001
Physician/provider	12,569 (13,047)	10,342 (13,496)	0.0465	6130 (8532)	3546 (6219)	0.0007	18,904 (22,769)	10,004 (16,315)	0.0008
Durable Medical Equipment	552 (1235)	327 (1003)	0.0293	466 (1049)	316 (1079)	0.1107	774 (1671)	574 (1866)	0.3394
Home Health Agency	1195 (2455)	872 (2659)	0.1425	1076 (2302)	689 (2186)	0.0431	1989 (3452)	1927 (3986)	0.8889
Hospice	0	147 (2304)	<0.0001	148 (1677)	317 (3032)	0.5235	4137 (8209)	6147 (12,873)	0.0317

**Table 3**

Inverse propensity score weighted models to study the association of HIV infection and outcomes, among, female, fee-for-service Medicare enrollees with primary breast cancer diagnosed between 2001 and 2011.

Covariate	Cox Proportional hazard Model All-cause mortality HR (95% CI)	Fine and Gray Model of competing risk Breast-cancer specific mortality HR (95% CI)	GLM model with log-link Phase-specific total cost of care					
			Initial phase		Interim phase		Terminal phase	
			Parameter Estimate (SE)	P value	Parameter Estimate (SE)	P value	Parameter Estimate (SE)	P value
<b>Model 1: Adjusted for all covariates*</b>								
HIV infected	2.99 (2.61, 3.43)	2.84 (2.29, 3.52)	0.1501 (0.0484)	0.0019	0.5888 (0.0688)	<0.0001	-0.0091 (0.0745)	0.9028
<b>Model 2: Summary stage groups*</b>								
<b>Localized</b>								
HIV infected	3.55 (2.87, 4.39)	2.22 (1.45, 3.41)	0.2313 (0.0575)	<0.0001	0.7000 (0.0787)	<0.0001	0.2102 (0.1180)	0.0749
<b>Regional/Distant</b>								
HIV infected	2.68 (2.24, 3.20)	2.98 (2.34, 3.78)	-0.0659 (0.0876)	0.4518	0.2695 (0.1381)	0.049	-0.2204 (0.0950)	0.1203
<b>Model 3: Reason for Medicare eligibility*</b>								
<b>Social Security Disability Insurance (SSDI)</b>								
HIV infected	3.02 (2.59, 3.53)	2.93 (2.32, 3.70)	0.1637 (0.0585)	0.0051	0.4675 (0.0843)	<0.0001	0.1098 (0.0882)	0.2129
<b>Age (65+)</b>								
HIV infected	1.09 (0.74, 1.61)	1.11 (0.54, 2.28)	0.0112 (0.1115)	0.9201	0.2867 (0.1539)	0.062	0.2106 (0.2601)	0.3067

\* adjusted for age at diagnosis, race/ethnicity (White, African American, Hispanic, Other), marital status (married, other), comorbidity score (<1, 1–2, 3, ≥4), reason for Medicare eligibility (disability, age 65+), census poverty track indicator (0%–5%, 5% to <10%, 10% to <20%, 20% to <100%), year of breast cancer diagnosis (2001–2003, 2004–2007, 2008–2011), summary stage (localized, regional/distant), treatment type. (surgery alone, surgery+ radiation, surgery + chemo, surgery + radiation + chemo, other (radiation alone, chemo alone, radiation + chemo), and, none).

4.5. Medicare eligibility criteria

We conducted separate analysis for the two subgroups based on Medicare eligibility criteria: age (65+) and SSDI disability (any age). The results of survival analysis are presented in Table 3. Among those who became Medicare eligible due to SSDI disability, HIV-infection was associated with higher hazard of all-cause mortality, compared to HIV-uninfected patients (HR=3.02, 95% CI=2.59, 3.53). However, among those who became eligible due to age, the hazard of all-cause mortality

did not differ by HIV infection status. We observed similar results for breast cancer-specific mortality, after accounting for competing risk.

5. Discussion

In this population-based study of fee-for-service, female Medicare enrollees with breast cancer, we observed impaired outcomes associated with HIV infection. Among HIV-infected patients, cost in initial phase was 16% higher and cost in interim phase was 80% higher, and

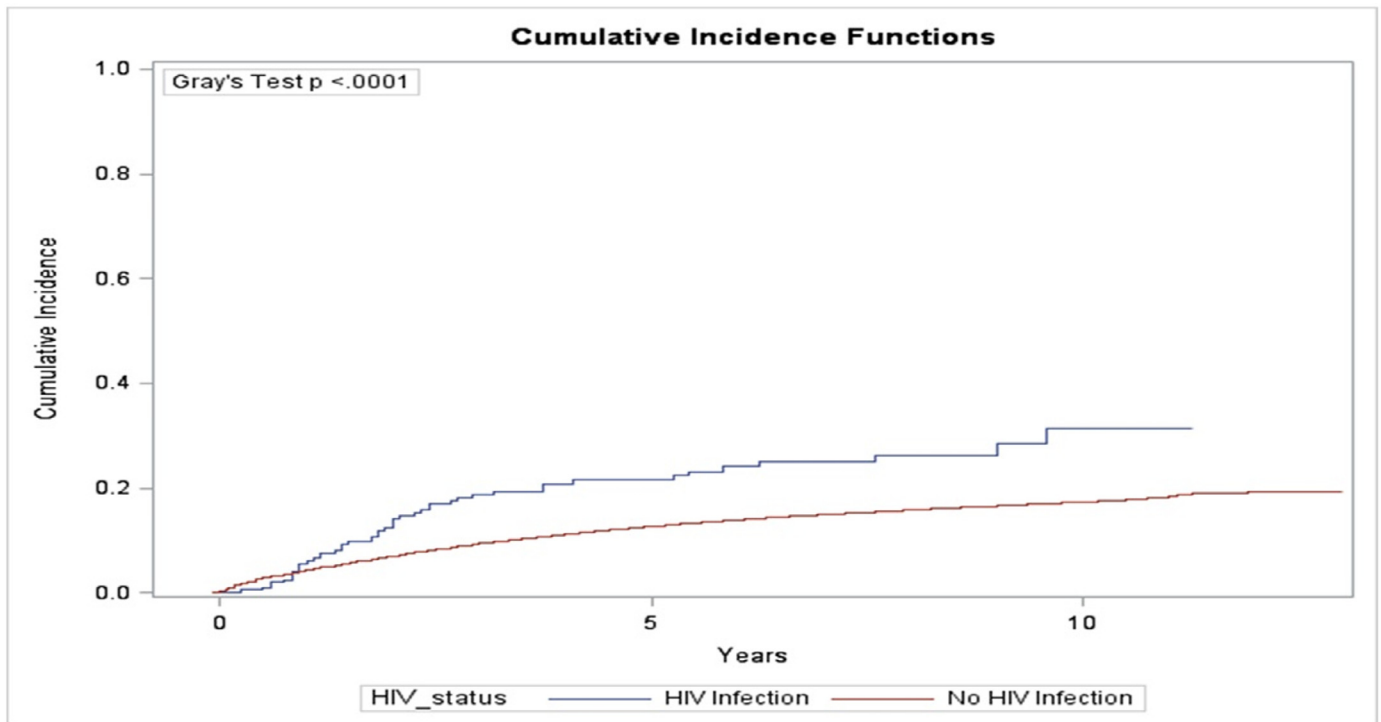


Fig. 2. Cumulative Incidence Function curve for breast cancer-specific mortality by HIV infection status among female, fee-for service Medicare enrollees with breast cancer.

the hazard of mortality (all-cause and breast cancer-specific) was at least twice as much, compared to HIV-uninfected patients. Across two sub-groups of cancer stage, all-cause mortality among HIV-infected patients remained elevated, compared to HIV-uninfected patients. For Medicare SSDI disabled patients, all-cause and breast cancer-specific mortality was higher for HIV-infected patients compared to HIV-uninfected patients. However, among patients whose Medicare eligibility was due to age, we observed no association between HIV infection and mortality.

HIV among female breast cancer patients has several implications. Concurrent comorbid conditions in HIV infected patients lead to substantially higher health service use and cost [21–25]. A study of Medicare enrollees with HIV observed that the percentage increase in median spending associated with cancer was 25% in year 2010 [25]. Using SEER-Medicare data, one study compared stage at diagnosis and survival between two groups of cancer patients younger than 65: disabled Medicare enrollees vs. others. Although cancer stage was comparable between the two groups, disabled Medicare patients had higher rates of cancer-related mortality for same stage of breast and colorectal cancer [26]. One study of eleven SEER Program tumor registries found that disabled women had higher breast cancer mortality rates. Disability status was associated with lower likelihood of receiving standard therapy after breast-conserving surgery, compared to other women. Additionally, the differential treatment pattern did not explain the disparity in breast cancer mortality rates [27]. A study of SEER-Medicare data and Social Security Administration disability group showed that demographic characteristics, treatments, and survival varied by type of disability groups. Women with mental disorders and neurological conditions had significantly lower adjusted rates of breast conserving surgery and radiation therapy, compared to non-disabled women [28].

In our study, we also observed higher hazard of mortality associated with HIV among breast cancer patients, similar to earlier research. Study using cancer and HIV/AIDS registries data showed that compared to HIV-uninfected patients, cancer-specific mortality was higher in HIV-infected patients for several cancers, including breast cancer, after adjusting for covariates. Patients with all ages and cancer stage were included in the study. Cox models showed that hazard of cancer-specific mortality was 2.61 (95% CI, 2.06 to 3.31) for HIV-infected patients, compared to HIV-uninfected patients [17]. A retrospective cohort study in Uganda included 802 patients, aged at least 18 years during diagnosis of breast cancer, cervical cancer, non-Hodgkin's lymphoma, Hodgkin's lymphoma, or esophageal cancer between 2003 and 2010 [20]. Patient's HIV status was assessed at baseline and vital status over one-year follow-up after cancer diagnosis. Patients with HIV-infection had two-fold or higher risk of mortality during the follow-up period compared to HIV-uninfected patients (HR 2.28, 95% CI 1.61–3.23). This association was valid for cancers with and without an infectious cause [20]. A study using National Cancer Database for the years 2004–2014 compared post-diagnosis mortality in 14 different cancers by HIV infection status. Among cancer patients of all ages and with disease stage I to III, HIV-infected patients had elevated mortality for 13 of the 14 cancer sites, including breast cancer (HR=1.85, CI=1.68–2.04). Persons with HIV had higher likelihood of being diagnosed with advanced-stage cancers and higher mortality in the post cancer diagnosis period [14]. A recent study compared overall mortality, cancer-specific mortality, and relapse or cancer-specific mortality after initial treatment in HIV-infected and HIV-uninfected cancer patients while accounting for receipt of specific cancer treatments. Study used SEER-Medicare data for patients aged  $\geq 65$  and diagnosed with non-advanced cancers of the colorectal, lung, prostate, or breast diagnosed between 1996 and 2012. HIV-infected patients with breast and prostate cancer had worse outcomes, compared to HIV-uninfected patients [19]. Another study analyzed the HIV/AIDS Cancer Match Study and the National Center for Health Statistics data (1996–2010). Overall mortality in patients with HIV and cancer was

significantly higher than expected mortality rates for each disease separately [18].

Several reasons may be leading to the poorer outcomes of care among female fee-for-service Medicare enrollees with concomitant breast cancer and HIV. Breast cancer patients with HIV present with late diagnosis of cancer [6, 7, 14]. In our study, the distribution of stage varied between HIV-infected and HIV-uninfected patients, with higher proportion of HIV-infected patients presenting with regional/distant stages, compared to HIV-uninfected patients. We found strong association between HIV infection and mortality across all stages of cancer. Although a large proportion of HIV-infected and HIV-uninfected patients received surgery (either alone or with radiation and/or chemo), the proportion of HIV-infected women who received surgery with chemo and/or radiation was higher than that of HIV-uninfected women. In our study, SSDI disabled patients were also more likely to receive combination therapy (surgery with radiation/chemotherapy). Studies indicate that in the presence of HIV, breast cancer patients have poorer response to chemotherapy [8, 15, 16]. Thus, our HIV-infected group may have had worse response to treatment. Additionally, presence of comorbidities, including breast cancer, was shown to increase the expenditure among HIV patients [21–25]. It appears that HIV as a comorbidity among breast cancer patients also leads to higher cost of care, as observed in our study.

Our study has strengths as well as limitations. Our cohort included all female fee-for-service Medicare enrollees with breast cancer. Thus, we were able to examine the incremental effects of HIV infection in younger, SSDI disabled enrollees and in elderly patients. Additionally, we obtained treatment information from SEER and Medicare claims to develop a comprehensive treatment profile for each patient. Medicare is an important source of health coverage for people with HIV. Medicare spending for HIV has increased over time, and the program is now the single largest source of federal financing for HIV care and treatment [37]. A person can become eligible for Medicare due to age (65+) or because of Social Security Disability Insurance (SSDI), after a two-year waiting period. Of fee-for-service Medicare enrollees with HIV-infection, nearly 79% are under age 65 [37]. Almost two third of our cohort was Medicare SSDI disabled. Breast cancer and HIV are among potentially qualifying health conditions for SSDI benefits. Another strength of our study is the attention to competing risks of death. We evaluated the hazard of breast cancer-specific death in the presence of competing risk of death from other causes. We used Fine and Gray models to evaluate the cumulative probability of death as well as hazard of mortality after adjusting for socio-demographic and clinical covariates. We were therefore able to obtain a clearer picture of the differences in the risk of breast cancer-specific death associated with HIV infection. Finally, our analytical strategy included inverse propensity weighted adjustment for all models, thus accounting for non-random assignment of breast cancer treatment.

Our study lacks HIV related data such as infection confirmation, length of infection, uptake of HIV treatment, and treatment adherence. Especially among Medicare SSDI disabled patients, HIV may be of longer duration and more aggressive in nature. At the same time, to classify a breast cancer case as HIV-infected, we did use an established algorithm [30, 38]. Additionally, SEER-Medicare does not have lifestyle data such as smoking status, obesity, exercise etc. Breast cancer patients have poorer response to chemotherapy in the presence of HIV infection, [8, 15, 16] however, we did not document these response. Our study sample consists of female, fee-for-service Medicare enrollees, not enrolled in HMO, with continuous prior coverage and living in a SEER region. Mortality rates derived from SEER data may not be representative of national cancer mortality rates.

In conclusion, our population-based study assessed the interaction of breast cancer, HIV infection, Medicare disability status, cancer stage and its implications for outcomes of care. Fee-for-service female enrollees with breast cancer experience impaired outcomes in the presence of HIV. Medicare is the single largest source of federal

financing for HIV care and treatment. Burden on Medicare will grow exponentially due to four trends: higher proportion of SSDI disabled among HIV-infected Medicare enrollees; longer survival among HIV-infected persons; increased incidence of HIV in older adults; and increased age related risk of breast cancer. However, currently no specific guidelines are available to address the management of concomitant breast cancer and HIV. Survivorship guidelines can benefit by understanding how characteristics of these two diseases interact and affect outcomes of care. Specifically, future research can focus on the pathways via which HIV infection affects cost and mortality. It will be also important to assess the optimal treatment regimen for HIV-infected breast cancer patients, as chemotherapy may lead to impaired outcomes in the presence of HIV. These research endeavors can lead to integrated strategies for effective management of concomitant breast cancer and HIV and inform survivorship care guidelines.

### Declaration of Competing Interest

The authors do not have any conflict of interests.

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### Supplementary materials

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