Breast Cancer Characteristics and Survival among Users versus Nonusers of Raloxifene

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ABSTRACT

Raloxifene reduces breast cancer incidence. However, it is unclear whether it also reduces mortality from breast cancer. For raloxifene to reduce incidence but not mortality, breast cancer survival would have to be worse for raloxifene users than nonusers. Surveillance Epidemiology and End Results-Medicare was used to identify women with invasive breast cancer diagnosed from 2007 to 2015 at ages 65–89 who had prior Medicare Part D (prescription drug) enrollment; breast cancer characteristics and survival were assessed among raloxifene regular users (≥180 days in past year) versus nonusers. Logistic regression was used to assess cancer characteristics. Two methods utilizing proportional hazards models were employed to assess breast cancer–specific survival. In method 1, survival was assessed adjusting for demographics, mammography use, and chronic conditions in the subset with Medicare fee-for-service enrollment. In method 2, predicted survival as a function of breast cancer characteristics was modeled in nonusers and the model applied to users to predict survival. A total of 116,317 raloxifene nonusers and 1,223 regular users were identified. Users were significantly more likely to have hormone receptor (HR)-negative cancers, but less likely to have T2+, N1+, and metastatic disease. There were 10,869 and 101 breast cancer–related deaths in nonusers and regular users, respectively. The HR (users vs. nonusers) for breast cancer–specific survival in method 1 was 0.94 (95% confidence interval, 0.73–1.22). In method 2, predicted survival was higher in users than nonusers (8-year survival 84.9% vs. 83.4%). Breast cancer–specific survival in raloxifene users was not worse than in nonusers, providing indirect evidence that raloxifene reduces breast cancer–related mortality.

Introduction

Selective estrogen receptor modulators (SERM), such as tamoxifen and raloxifene, have been shown to reduce the incidence of invasive breast cancer (1–7). Originally in 2013 and updated in 2019 to include aromatase inhibitors, the U. S. Preventive Services Task Force (USPSTF) continues to recommend, with a "B" rating, the use of SERMs for breast cancer risk reduction in women at high breast cancer risk and at low risk for adverse medication effects (8, 9). Tamoxifen was evaluated for its preventive efficacy in four prospective, randomized trials that tested the drug's ability to reduce first primary breast cancers in high risk women: the National Surgical Adjuvant Breast and Bowel Project (NSABP) Prevention (P)-1:BCPT; the Royal Marsden Hospital tamoxifen randomized chemoprevention trial; the Italian Tamoxifen Prevention Study; and the International Breast Cancer Intervention Study-I (1–4). The combined data indicated an overall 30%–40% reduction in breast cancer incidence following 5 years of tamoxifen versus placebo.

Raloxifene was evaluated in the Multiple Outcomes of Raloxifene Evaluation (MORE) randomized trial in postmenopausal women with osteoporosis, in an extension of the MORE trial, Continuing Outcomes Relevant to Evista, and in the Raloxifene Use for the Heart trial (5–7). A meta-analysis of these trials showed a significant, 56% reduction in invasive breast cancer incidence with raloxifene compared with placebo (10). The successful raloxifene trials led to the NSABP P-2: Study of Tamoxifen and Raloxifene (STAR) trial to directly test raloxifene versus tamoxifen. The initial analysis of STAR (3.9 years mean follow-up) showed no difference in the incidence of invasive breast cancer between raloxifene and tamoxifen, but less noninvasive breast cancer with tamoxifen (11). The extended follow-up (median 81 months) showed a significantly higher incidence of invasive breast cancer with raloxifene compared with tamoxifen [rate ratio (RR), 1.24; 95% confidence interval (CI), 1.05–1.47; ref. 12].

In addition, these studies and STAR in particular demonstrated important differences in adverse events, including fewer uterine cancers and less venous thromboembolic events (specifically pulmonary emboli and deep vein thrombosis) with raloxifene than with tamoxifen (12).

The SERM trials showing reduced breast cancer incidence were too small and of too short duration to examine mortality, and in fact, some have criticized the trials for this shortcoming, despite the enormous additional resources that assessing a mortality endpoint would have required (13, 14). The trial

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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evidence suggests that SERMs primarily prevent hormone positive, and thus on average, less aggressive tumors. Thus it remains uncertain whether SERMs reduce mortality from breast cancer. The USPSTF recommendation statement concluded that "whether reductions in breast cancer incidence lead to a corresponding reduction in mortality is unclear" (8).

Given the reduction in breast cancer incidence with SERMs, a lack of a corresponding mortality reduction would indicate that only those cancers not destined to be fatal are prevented by SERMs. If that were the case, those breast cancers that did develop in users would need, on average, to contain a higher proportion of fatal cases than in the overall (or non-SERM using) population, as seen in **Fig. 1**. Assuming an overall incidence reduction of 40% with SERMs, and a 20% case-fatality rate among non-SERM-users, to achieve the non-SERM rate of fatal breast cancer in the SERM group, a case-fatality rate of 33% would be needed. In contrast, with the same case-fatality rate in the two groups, the reduction in incidence of fatal disease in the SERM versus non-SERM group would be the same as the reduction in overall incidence.

In this article, we use the Surveillance Epidemiology and End Results (SEER)-Medicare database to compare breast cancer characteristics and survival in women exposed versus unexposed to raloxifene prior to breast cancer diagnosis. We concentrate on raloxifene because use of tamoxifen before breast cancer diagnosis is very low (around a tenth the rate of raloxifene, which itself is relatively infrequent; ref. 10). By comparing breast cancer characteristics and survival among users and nonusers, we attempt to determine whether and to what extent breast cancers occurring in raloxifene users have a worse prognostic profile than those in nonusers. Without sufficient data to assess mortality rates directly, we use tumor characteristics and survival to indirectly assess the impact of raloxifene on breast cancer–related mortality. If, for example, raloxifene users are found to have better or similar survival as nonusers, one would expect a corresponding decrease in breast cancer–related mortality, along with the decrease in incidence, with raloxifene use.

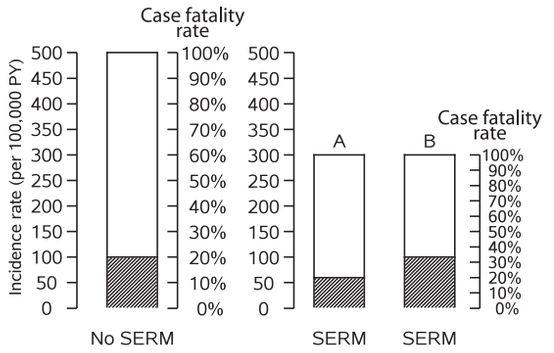

Figure 1.

Incidence rates, Case fatality rates, and mortality reduction. Total height of bars reflect overall incidence in the group (SERM or no SERM); shaded parts of bars reflects incidence of fatal disease (disease destined to be fatal). The fatal disease RR (RR_{FD}) for SERM versus no SERM is approximately the incidence RR (RR_I) times the case fatality RR (RR_{CF}). Given an RR_I of 0.6, or a 40% incidence reduction in the SERM versus no SERM group (300 vs. 500), equal case fatality rates, of 20%, in each group ($RR_{CF} = 1.0$) give the same 40% reduction in fatal disease ($RR_{FD} = 0.6$), 60 versus 100 (bar **A**). A case fatality rate of 33.3% in the SERM group, $RR_{CF} = 1.67$, leads to a RR_{FD} of 1.0 (1.67×0.6), or no reduction in fatal disease (bar **B**). SERM is selective ER modulator.

Materials and Methods

The SEER-Medicare database merges data on cancer incidence, characteristics, and survival from SEER with Medicare Part A&B claims data and Part D prescription drug data (https://healthcaredelivery.cancer.gov/seermedicare). Part D data, available starting in 2007, includes drug name, prescription fill-date, dose, quantity dispensed, and days' supply. For raloxifene, dose was always 60 mg and quantity dispensed equal to days' supply. A raloxifene days of use variable was created for given time periods by summing up days' supply over all prescriptions filled during the period.

The analysis cohort included all women in SEER-Medicare diagnosed with invasive breast cancer from 2008 to 2015 who were ages 65–89 at diagnosis and had Part D coverage for the entire year (12-month period) prior to diagnosis. A raloxifene regular user was defined as a woman with $\geq$180 days of raloxifene use in the year prior to diagnosis, while a nonuser was defined as a woman with no use (no prescriptions filled) during that period; irregular users had 1–179 days use. In addition, to increase the maximum follow-up time for the analysis of survival, we also included women diagnosed in 2007 with at least 6 months of Part D enrollment and who either had $\geq$180 days of use (regular user) or no use (nonuser) prior to diagnosis. Survival data, including underlying cause of death, were available through 2015.

In addition to Part D data, SEER-Medicare contains information on medical procedures (and related diagnoses) and chronic disease conditions. These factors may be related both to raloxifene use and breast cancer survival and are thus potential confounders of this relationship. The primary procedure of interest as a potential confounder is screening mammography; chronic conditions of interest include osteoporosis, Alzheimer/dementia, congestive heart failure, diabetes, chronic obstructive pulmonary disease (COPD), stroke/myocardial infarction, and chronic renal disease.

Only women with Medicare fee-for-service coverage had complete claims information available in SEER-Medicare on procedures and chronic conditions. Therefore, in addition to the overall Part D analysis cohort (PDC), we defined a subcohort of women with Part B (fee-for-service) coverage for the entire 24-month period prior to diagnosis, denoted as the Part D&B cohort (PDBC). Information on screening mammography was available from outpatient and carrier Medicare files; information on chronic diseases was available from the yearly chronic condition variables (variables predefined by CMS algorithms based on procedure and International Classification of Diseases codes).

For the PDBC, we defined undergoing regular mammography screening as, having had 1+ screening mammogram in the 24-month period prior to diagnosis. Screening mammograms consisted of Healthcare Common Procedure Coding System (HCPCS) procedure codes 76092, 77052, 77057, and G0202. For the PDBC, a breast cancer case was denoted as screen-detected if the woman had a screening mammogram within 6 months of diagnosis.

The breast cancer cases here were not restricted to first primary cases (i.e., for some cases the woman had a prior invasive breast cancer). As a sensitivity analysis, we reran the major findings restricted to first primary cases.

Statistical analysis

We used logistic regression to assess the relationship between raloxifene use and tumor characteristics. Three types of OR were computed as follows: (i) raw ORs (PDC), (ii) adjusted ORs (PDC), and (iii) adjusted ORs (PDBC). Adjusted ORs were adjusted for race/ethnicity (non-Hispanic white, black, and other), age at diagnosis (5-year age group), diagnosis year, and SEER registry.

We utilized two approaches to assess the relationship between raloxifene use and breast cancer–specific survival. In method 1, observed breast cancer survival in users versus nonusers was compared, controlling for potential confounders. In method 2, breast cancer–specific survival was modeled as a function of only breast cancer characteristics (and demographics) using data from nonusers alone, and the resulting fitted model was then applied to raloxifene users. For both methods, the primary analysis was comparing regular users to nonusers. As a secondary analysis, we also compared all users (regular and irregular) with nonusers.

The two methods are complementary. The first uses observed data in both groups, which is preferable over modeling; however, there is the possibility of unmeasured confounders, that is, variables unavailable in SEER-Medicare that may be related both to raloxifene use and survival. The second uses modeling instead of observed data for users; however, it circumvents the issue of confounding because it does not involve observed survival in users.

Multivariate proportional hazards models were used for both methods. For method 1, covariates included age, race/ethnicity, diagnosis year, SEER registry, regular screening mammography, and chronic conditions. We also included bisphosphonate use (in the year prior to diagnosis), because raloxifene and bisphosphonates are both used to treat osteoporosis and bisphosphonate use may be related to breast cancer survival. This full model was run on the PDBC, because only those subjects had these covariates available. For comparison, we also ran the model with only the demographic covariates of age, race, diagnosis year, and SEER registry (restricted model). We additionally ran the model for the outcome of overall survival instead of breast cancer–specific survival. For the models with breast cancer–specific survival, women dying of other causes were censored at time of death.

For method 2, the multivariate model included the following cancer characteristics: tumor–node–metastasis stage components, tumor grade, estrogen receptor (ER), progesterone receptor (PR), HER2, plus age, race, and diagnosis year. After fitting the model on PDC nonusers, the parameterized model was applied to the cancer (and demographic) characteristics of PDC regular users and averaged to obtain a predicted survival curve for users. The parameterized model was also applied to nonusers' characteristics to derive a predicted survival curve for nonusers. Predicted survival rates for each group were age, race, and calendar-year adjusted to the overall cohort distribution to compute demographics-adjusted predicted survival rates. Bootstrapping was used to generate 95% CIs for differences in predicted survival for users versus nonusers. Mode of detection was available only for PDBC women; therefore, we also performed the above modeling exercise on the PDBC including mode of detection.

Results

Of 321,334 women in SEER-Medicare diagnosed with invasive breast cancer from 2007 to 2015, 205,643 were ages 65–89 at diagnosis. Of these, 117,840 (57%) had Part D coverage for the entire 12-month period before diagnosis (6-month period for those diagnosed in 2007) and constituted the PDC. Of the 117,840, 116,317 (98.7%) were raloxifene nonusers, 1,223 (1.0%) were regular users and 300 irregular users. The PDBC consisted of 53,792 women, 52,960 (98.4%) nonusers, 681 (1.3%) regular users, and 151 (0.3%) irregular users.

Days of raloxifene use

Median (25th/75th) days of raloxifene use for PDC regular users in the year before diagnosis was 330 (270/360), or 90% of the year. For women with complete part D coverage for the 24-, 36-, and 60-month periods before diagnosis ($n = 894$, $n = 663$, and $n = 327$, respectively), median days of use over these periods was 660, 990, and 1530, respectively, comprising 90%, 90%, and 84% of the period. Conversely, for nonusers, among those with Part D coverage for the entire 36-month ($n = 68{,}339$) or 60-month period ($n = 37{,}764$) before diagnosis, 99.4% and 98.8%, respectively, had no raloxifene use for the entire period. Irregular users had median 90 days of use in the prior year, and among those with complete part D coverage for the 36-month period prior to diagnosis ($n = 161$), median days of use was 320 (29% of the period).

Demographics and breast cancer characteristics

Table 1 shows demographics and medical history for the PDC and PDBC. In the PDC, regular users were less likely to be non-Hispanic black (3.3% vs. 9.7%), were slightly older at diagnosis (median age 75 vs. 74) and were more likely to be diagnosed in 2007–2011 (56.6% vs. 46.2%) than nonusers.

Table 1. Demographic and medical history by raloxifene use category.

	PDC		PDBC	
	Nonuser ***n*** **= 116,317**	**Regular user** ***n*** **= 1,223**	**Nonuser** ***n*** **= 52,960**	**Regular user** ***n*** **= 681**
Median age at diagnosis (25th/75th)	74 (70/80)	75 (70/80)	76 (71/81)	76 (72/81)
Race/ethnicity				
White non-Hispanic	94,908 (81.6)	1,005 (82.2)	45,226 (85.4)	577 (84.7)
Black non-Hispanic	11,276 (9.7)	40 (3.3)	4,328 (8.2)	[a]
Hispanic	2,216 (1.9)	15 (1.2)	809 (1.5)	[a]
Asian	4,054 (3.5)	81 (7.0)	1,386 (2.6)	45 (6.9)
Other/unknown	3,863 (3.3)	82 (6.9)	1,211 (2.4)	[a]
Year of diagnosis				
2007–2011	53,753 (46.2)	692 (56.6)	25,327 (47.8)	391 (57.4)
2012–2015	62,564 (53.8)	531 (43.4)	27,633 (52.2)	290 (42.6)
Bisphosphonate use	14,314 (12.3)	119 (9.7)	6,568 (12.4)	64 (9.4)
Regular screening mammograms	—	—	40,917 (77.3)	543 (79.7)
Chronic conditions	—	—		
Osteoporosis	—	—	8,259 (15.6)	235 (34.5)
COPD	—	—	7,784 (14.7)	78 (11.5)
Stroke/myocardial infarction	—	—	2,939 (5.6)	22 (3.2)
Chronic renal disease	—	—	9,155 (17.3)	91 (13.4)
Alzheimer/dementia	—	—	6,050 (11.4)	65 (9.5)
Diabetes	—	—	17,323 (32.7)	169 (24.8)
Congestive heart failure	—	—	10,071 (19.0)	96 (14.1)

[a]Too few in cell to specify.

Regular users were slightly less likely to use bisphosphonates than nonusers (9.7% vs. 12.3%). These associations also generally held in the PDBC. The PDBC overall was more non-Hispanic white and slightly older than the PDC.

In the PDBC, regular users were substantially more likely to have osteoporosis than nonusers (34.5% vs. 15.6%), but modestly less likely to have other chronic conditions. Regular screening mammography use was slightly higher among regular users (79.7%) than nonusers (77.3%).

Table 2 shows breast cancer characteristics by raloxifene use category. For tumor markers, regular users were more likely than nonusers to be ER-negative (21.9% vs. 14.1%), PR-negative (41.5% vs. 26.4%), and hormone receptor–negative (20.6% vs. 13.3%). Regular users were also slightly less likely to be HER2 negative (83.1% vs. 86.8%) and more likely to be grade III/IV (31.5% vs. 26.0%). Regular users had lower T stage, less node-positive disease, and less metastatic disease. For example, for regular users versus nonusers, 25.9% versus 35.3% were T2+, 18.4% versus 24.8% were N1+, and 3.4% versus 5.5% had metastatic disease. Rates of surgery were high for both groups, but slightly higher for regular users (92.7%) than nonusers (88.1%). ORs were generally similar between raw PDC ORs, adjusted (for demographics) PDC ORs, and adjusted PDBC ORs. The proportion of cases that were screen detected was similar in PDBC regular users (60.0%) and nonusers (59.3%).

Breast cancer–related deaths and survival

There were 101 (8.3%) and 10,869 (9.3%) breast cancer–related deaths among PDC regular users and nonusers, respectively; breast cancer–specific 5- and 8-year survival rates were 89.2% and 87.1% for regular users versus 87.1% and 83.6% for nonusers. In the PDBC, breast cancer–related deaths numbered 59 (8.7%) and 5,302 (10.0%) for regular users and nonusers, respectively, with 5- and 8-year breast cancer–specific survival rates of 88.7% and 84.8% (regular users) versus 86.3% and 82.7% (nonusers). For the analysis of breast cancer–specific survival in method 1, **Table 3** shows the results of the model examining breast cancer–specific survival as a function of raloxifene use, demographics, and medical history in the PDBC. The hazard ratio (HR) for regular raloxifene users versus nonusers was 0.94 (95% CI, 0.73–1.22). For comparison, the restricted model (controlling for demographics only) showed an HR 0.80 (95% CI, 0.62–1.04). The HR for all users (regular and irregular) versus nonusers for the full model was 1.005 (95% CI, 0.80–1.26).

Examining the effect of covariates, the HR was significantly below one for regular screening mammography (HR = 0.38; 95% CI, 0.35–0.40). HRs were significantly elevated for most chronic conditions, except osteoporosis, whereas osteoporosis, and bisphosphonate use, each showed HRs significantly below 1.0 (HRs = 0.80 and 0.77, respectively; **Table 3**). Among women without any evidence of osteoporosis, that is, without reported osteoporosis or bisphosphonate use, who comprised 62% and 77% of regular users and nonusers, respectively, the HR for regular users versus nonusers was 0.84 (95% CI, 0.59–1.17).

With respect to overall survival, for the PDBC there were 149 (21.9%) and 13,247 (25.0%) total deaths for regular users and nonusers, respectively, giving 8-year all-cause survival rates of 59.1% and 54.0%. The HR for regular users versus nonusers was 0.90 (95% CI, 0.76–1.06) for the full model and 0.78 (95% CI, 0.67–0.92) for the restricted model.

Table 2. Breast cancer characteristics by raloxifene use category.

Tumor characteristic	Nonuser $n = 116,317$	Regular user $n = 1,223$	PDC Raw OR[a]	PDC Multivariate OR[b]	PDBC Multivariate OR[b]
Histology					
Ductal	80,027 (68.8)	831 (68.0)	Reference	Reference	Reference
Lobular	12,400 (10.7)	129 (10.6)			
Mixed ductal and lobular	6,437 (5.5)	73 (6.0)	1.04 (0.93–1.18)	1.04 (0.93–1.18)	1.10 (0.93–1.29)
Other	17,453 (15.0)	190 (15.5)			
ER status[c]					
Positive	94,011 (85.9)	908 (78.1)	Reference	Reference	Reference
Negative	15,470 (14.1)	255 (21.9)	1.70 (1.48–1.96)	1.76 (1.53–2.03)	1.73 (1.42–2.10)
Unknown	6,836	60			
PR status[c]					
Positive	80,146 (73.6)	679 (58.5)	Reference	Reference	Reference
Negative	28,722 (26.4)	481 (41.5)	1.99 (1.77–2.23)	2.02 (1.79–2.27)	2.11 (1.80–2.47)
Unknown	6,879	61			
Hormone receptor status					
Positive	94,896 (86.7)	923 (79.4)	Reference	Reference	Reference
Negative	14,558 (13.3)	239 (20.6)	1.69 (1.46–1.95)	1.75 (1.52–2.02)	1.74 (1.43–2.11)
Unknown	6,863	61			
HER2 status					
Positive	8,801 (10.9)	108 (13.9)	Reference	Reference	Reference
Negative	70,316 (86.8)	647 (83.1)	0.75 (0.61–0.92)	0.74 (0.61–0.91)	0.81 (0.61–1.08)
Borderline	1,892 (2.3)	24 (3.1)			
Unknown	35,308	444			
Grade					
I	28,819 (27.0)	300 (26.6)	Reference	Reference	Reference
II	49,988 (46.9)	472 (41.9)			
III/IV	27,798 (26.0)	355 (31.5)	1.30 (1.15–1.48)	1.33 (1.18–1.52)	1.30 (1.09–1.54)
Unknown	9,712	96			
T stage					
T0/Tis	578 (0.5)	17 (1.5)			
T1A	8,193 (7.5)	120 (10.3)	Reference	Reference	Reference
T1B	22,034 (20.0)	278 (23.9)			
T1C	38,390 (34.9)	413 (35.5)			
T2	29,266 (26.6)	244 (21.0)			
T3	4,920 (4.5)	33 (2.8)	0.64 (0.56–0.73)	0.65 (0.56–0.74)	0.68 (0.57–0.81)
T4	4,625 (4.2)	24 (2.1)			
Unknown	6,402	60			
Nodal status					
None	83,745 (75.3)	963 (81.6)	Reference	Reference	Reference
N1	19,988 (18.0)	158 (13.4)	0.69 (0.59–0.80)	0.70 (0.60–0.81)	0.76 (0.63–0.93)
N2–N3	7,513 (6.8)	59 (5.0)			
Unknown	5,071	43			
Metastatic					
Yes	6,228 (5.5)	40 (3.4)	0.60 (0.43–0.82)	0.61 (0.44–0.84)	0.59 (0.39–0.90)
No	106,153 (94.5)	1,146 (96.6)	Reference	Reference	Reference
Unknown	3,936	37			
Surgery[d]					
Yes	102,427 (88.1)	1,134 (92.7)	Reference	Reference	Reference
No	13,890 (11.9)	89 (7.3)	0.60 (0.48–0.75)	0.61 (0.49–0.77)	0.61 (0.46–0.82)
Screen detected					
Yes	38,180 (59.3)	474 (60.0)	1.02 (0.89–1.18)	1.14 (0.98–1.32)	1.16 (0.98–1.36)
No	26,161 (40.7)	317 (40.0)	Reference	Reference	Reference
Unknown	51,976	432			

Note: Percentage for categories exclude unknowns.

[a]OR is for regular users versus nonusers. Reference group may include multiple categories, as indicated by the number of rows in the Reference box (e.g., for grade, I and II is reference, III and IV is comparison group).

[b]Multivariate OR (regular users vs. nonusers adjusted for age, race, year of diagnosis, and SEER registry).

[c]Negative includes a small number of borderline cases.

[d]No category includes a small percentage of unknown cases.

Table 3. Proportional hazards model of breast cancer–specific survival in raloxifene regular users and nonusers in the PDBC.

	HR (95% CI)
Raloxifene nonuser	Reference
Raloxifene regular user	0.94 (0.73–1.22)
White (non-Hispanic)	Reference
Black	1.34 (1.2–1.4)
Other	1.01 (0.9–1.2)
Age 65–69	Reference
Age 70–74	1.02 (0.9–1.2)
Age 75–79	1.09 (0.98–1.2)
Age 80–84	1.36 (1.3–1.5)
Age 85–89	1.82 (1.7–2.1)
Regular screening mammography	0.38 (0.35–0.40)
Bisphosphonate use	0.77 (0.72–0.85)
Osteoporosis	0.80 (0.71–0.86)
Alzheimer/dementia	2.07 (1.9–2.2)
Diabetes	1.01 (0.94–1.1)
COPD	1.30 (1.2–1.4)
Chronic renal disease	1.55 (1.5–1.7)
Stroke/myocardial infraction	1.10 (0.99–1.2)
Congestive heart failure	1.43 (1.3–1.5)

For method 2, the multivariate model of survival (fit on nonusers) showed significant elevated hazards for ER-negative, PR-negative, and higher grade tumors. In addition, higher T stage, positive nodes, and metastatic disease showed significantly elevated HRs (Supplementary Table). **Table 4** shows the results of applying the fitted model to raloxifene regular users (and nonusers) to obtain predicted survival (adjusted for demographics). For the PDC, predicted breast cancer–specific survival rates in regular users versus nonusers were 87.9% versus 86.6% at 5 years and 84.9% versus 83.4% at 8 years. The difference in survival, regular users minus nonusers, was 1.3% (95% CI, −0.3%–2.6%) at 5 years and 1.5% (95% CI, −0.3%–2.8%) at 8 years. Results for the PDBC were similar; differences in 5- and 8-year survival were 1.8% (95% CI, 0.1%–3.4%) and 2.0% (95% CI, 0.1%–3.7%; **Table 4**).

As noted above, the cases here were not restricted to first primary invasive breast cancers. However, the results were similar when restricting the analyses to first primary cases. For example, the method 1 breast cancer–specific HR for regular users versus nonusers (full model) was 0.93 (95% CI, 0.70–1.23). In addition, the method 2 predicted 8-year breast cancer–specific survival rates in the PDC were 83.5% for nonusers and 85.4% for regular users, with a difference of 2.0%.

Discussion

Among women diagnosed with breast cancer from 2007 to 2015 in SEER-Medicare, prior use of raloxifene was infrequent, about 1%, reflecting primarily the low use of raloxifene overall among women in this age group (65+). Raloxifene users were found to have a higher proportion of ER-negative (and PR-negative) tumors than nonusers, which is consistent with the prior evidence that raloxifene prevents primarily ER-positive tumors (10). Raloxifene users also had a modestly higher frequency of high-grade tumors than nonusers. However, users also had a lower proportion of higher stage tumors (T2+, N1+, and metastatic) than nonusers. With respect to survival, the direct examination of breast cancer–specific survival in the full model controlling for potential confounders (e.g., comorbidities, regular mammography use) showed no elevated hazard for regular users, with an HR for users slightly, although not significantly, below one (HR = 0.94; 95% CI, 0.73–1.22). A lower HR (0.84) was observed in the restricted model, which controlled for demographics alone, indicating that the other covariates were confounding the association between raloxifene use and survival in that model. Among women without evidence of osteoporosis, there was also no elevated hazard for regular users (HR = 0.84; 95% CI, 0.59–1.17 in the full model). The indirect approach to assessing survival predicted modestly increased survival (1%–2%) in users compared with nonusers, with lower 95% CI of 0.1% (PDBC) to −0.3% (PDC). The breast cancer survival model utilized in this approach produced results reflecting the general consensus on prognostic factors, with ER- and PR-negative tumors, T2+, N1+, and metastatic tumors having worse survival (15–16). Screen-detected tumors had substantially better prognosis; the prevalence of these, however, was similar among users and nonusers.

To demonstrate that raloxifene reduces breast cancer–related mortality it is sufficient to show that breast cancer–specific survival is not worse among raloxifene users. Moreover, as illustrated in **Fig. 1**, the RR for breast cancer–related mortality is approximately equal to the incidence RR times the case fatality RR, so even a modestly decreased survival among users could be consistent with a mortality reduction, albeit one with a lower magnitude than the incidence reduction. The survival point

Table 4. Predicted breast cancer–specific survival in raloxifene regular users and nonusers.

		PDC		PDBC	
Survival statistic	**Group**	**5-Year**	**8-Year**	**5-Year**	**8-Year**
Predicted survival (age/race/calendar-year adjusted)[a]					
	Regular users	87.9%	84.9%	87.6%	84.5%
	Nonusers	86.6%	83.4%	85.8%	82.5%
Difference in predicted survival[a]					
	Regular users minus nonusers	1.3% (−0.3 to 2.6)	1.5% (−0.3 to 2.8)	1.8% (0.1–3.4)	2.0% (0.1–3.7)

[a]Adjusted to overall cohort distribution of age, race, and calendar year.

estimates found here indicate no worse, or marginally improved, survival in users, indicating a likely mortality reduction of similar magnitude as the incidence reduction.

However, the precision of the survival estimates must also be considered. A "worst-case" scenario for a raloxifene mortality benefit would be a true survival HR of 1.22 (upper 95% CI) in the direct approach or a true 0.3% worse survival (lower 95% CI) in the indirect approach. Taking the survival HR as a proxy for the case fatality RR, an HR of 1.22 would still indicate a mortality reduction, with a mortality RR of 0.73 (1.22×0.6), assuming a 40% incidence reduction. The 0.3% worse survival translates into an HR of about 1.03, indicating a mortality reduction only slightly lower than the incidence reduction. Therefore, considering both the point estimates and their precision, raloxifene likely confers a substantial reduction in breast cancer–related mortality.

This study utilized a standardized population database of breast cancer cases (SEER) and identified a relatively large number of women using raloxifene prior to diagnosis. In addition, past drug usage was well described, and showed that regular users were prescribed raloxifene for about 90% of their Part D covered days (on average) through the 5-year prediagnosis period. The two major raloxifene versus placebo trials had protocols of 3–5 years on drug, so regular users here had at least as long use as in those trials (5–7).

A limitation of this analysis was that follow-up for survival was only 8.5 years. Analysis of SEER survival data, however, shows that about 75% of breast cancer–related deaths occurred within the first 8 years (17). Studies have shown that the relative hazard for breast cancer–related death for ER-positive versus -negative tumors is dependent on time from diagnosis, with ER-negative tumors having higher hazard for around the first 8 years and ER-positive tumors having higher hazard thereafter (18). Therefore, to the extent that raloxifene users were more likely to have ER-negative tumors, the relatively short follow-up duration favors nonusers. Additional follow-up time will allow determination whether these observations are maintained. Another limitation is that the analysis was restricted to women enrolled in Medicare Part D. However, such enrollment ranged from 56% in 2008 to 72% in 2017, so this is not a highly selected population (19). In addition, the analysis was limited to women aged 65+; thus, these data are not informative for younger women newly reaching postmenopausal status.

Use of raloxifene for breast cancer risk reduction is low (20). Various reasons for this on both the patient and provider side have been proposed (13, 21–22). One potential reason is a concern about whether raloxifene actually prevents breast cancer–related mortality as well as incidence. Mammography, while reducing breast cancer–related mortality by 15%–30%, also substantially increases the risk of being diagnosed with breast cancer due to overdiagnosis (23). In contrast, if raloxifene reduces incidence by around 40%, and reduces mortality by a similar magnitude, the benefit to harms profile of raloxifene starts to look comparable with that of mammography. Clearly, long-term usage of a potent drug is different from undergoing annual or biennial radiographic screenings, but raloxifene should be part of the conversation for women at high risk of breast cancer, especially among postmenopausal women who need osteoporosis therapy or are at risk for osteoporosis.

In conclusion, among women with invasive breast cancer, those regularly using raloxifene prior to diagnosis had similar breast cancer–specific survival as those not using raloxifene, suggesting that raloxifene may reduce breast cancer–related mortality as well as incidence.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.F. Pinsky
Development of methodology: P.F. Pinsky
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.F. Pinsky
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.F. Pinsky, E.A. Miller, B.M. Heckman-Stoddard
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