HHS Public Access

Author manuscript

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2024 April 02.

Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2023 October 02; 32(10): 1302–1311.

doi:10.1158/1055-9965.EPI-23-0421.

Adverse Health Outcomes Among Rural and Urban Breast Cancer Survivors: A Population-Based Cohort Study

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Abstract

Background: Limited population-based studies have focused on breast cancer survivors in rural populations. We sought to evaluate the risk of adverse health outcomes among rural and urban breast cancer survivors and to evaluate potential predictors for the highest risk outcomes.

Methods: A population-based cohort of rural and urban breast cancer survivors diagnosed between 1997 and 2017 was identified in the Utah Cancer Registry (UCR). Rural breast cancer survivors were matched on year (±1 year) and age at cancer diagnosis (±1 year) with up to 5 urban breast cancer survivors (2,359 rural breast cancer survivors; 11,748 urban breast cancer survivors). Cox proportional hazards models were used to calculate hazard ratios (HRs) with 99% confidence intervals (CI) for adverse health outcomes overall, within 5 years, and >5 years after cancer diagnosis.

Results: Compared to urban breast cancer survivors, rural breast cancer survivors had a 39% (HR = 1.39, 95%CI 1.02, 1.65) higher risk of heart failure (HF) within the 5 years of follow-up.

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Conflict of Interest: The authors declare no conflicts of interest.

Overall, there was no increase in the risk of other adverse health outcomes. A higher baseline body mass index and Charlson Comorbidity Index, family history of cardiovascular diseases, family history of breast cancer, and advanced cancer stage were risk factors for HF for rural and urban breast cancer survivors, with similar levels of HF risk.

Conclusions: Rural residence was associated with an increased risk of HF among breast cancer survivors.

Impact: Our study highlights the need for primary preventive strategies for rural cancer survivors at risk of heart failure.

Keywords

rural residence; breast cancer; adverse outcomes; cancer survivorship; matched-cohort

Introduction

Approximately 19.3% of Americans with cancer live in rural areas.[1] There is overwhelming evidence that rural cancer patients are challenged with higher risks of various adverse health outcomes than their urban counterparts.[2–5] A number of studies reported an increased risk of cardiovascular disease,[6,7] diabetes,[8] anxiety, depression, suicide,[9] or osteoporosis[10] in breast cancer survivors compared with women without cancer. In addition, treatment-induced ocular toxicity and ototoxicity were suggested in breast cancer patients due to a change in estrogen level from the breast cancer treatments.[11–13] However, to our knowledge, fewer health outcome studies have been reported of breast cancer survivors in rural communities. Studies focusing on distance to healthcare reported a higher likelihood of patients receiving mastectomy compared to lumpectomy in rural areas,[14] and a higher likelihood of patients forgoing radiation in part due to lack of rural treatment facilities.[15] Other studies reported on higher stage at diagnosis in rural breast cancer survivors,[16] and higher odds of heart failure among older rural cancer survivors.[17]

Rural populations are older, with higher poverty levels, and lack access to insurance and health care resources.[18,19] Given that breast cancer survival continues to increase,[20] and given the lack of large-scale population-based health outcome studies in rural breast cancer survivor populations, continued understanding of health outcomes in rural populations will result in support for the management of care in breast cancer patients. Thus, the aim of our study was to assess the risk of adverse health effects among rural compared to urban breast cancer survivors and to evaluate potential risk predictors for the highest risk outcomes.

Methods

Study Population

This study cohort included women identified in the Utah Cancer Registry (UCR) diagnosed with first primary breast cancer (primary site ICD-O-3 C50.0 to C50.9). Inclusion criteria were that the breast cancer survivor was a Utah resident, aged ≥18 years at cancer diagnosis, diagnosed between 1997 and 2017, and survived for at least one year after breast cancer diagnosis. Rural breast cancer survivors were matched on cancer diagnosis year (±1 year)

and age at cancer diagnosis (±1 year) with up to 5 urban breast cancer survivors. A total of 27 rural and 3 urban survivors were excluded for unknown cancer stage. A total of 2,359 rural breast cancer survivors and 11,748 urban breast cancer survivors were included in this study.

Data Source and Study Variables

The UCR is the statewide, population-based cancer registry for Utah. All cancer survivors from the UCR are linked to the Utah Population Database (UPDB).[21,22] The UPDB uses record linking IBM® InfoSphere® QualityStage software to perform probabilistic records linking to various databases, including the UCR. The UPDB records included demographic, Utah driver's license, statewide vital, and family history information linked to medical records. Variables from the UCR included race, ethnicity, residence at cancer diagnosis, birth year, age at cancer diagnosis, cancer treatment receipt histology, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor (HER2) status (available starting in 2010), and cancer stage at diagnosis. Within the UPDB, the cancer data is based on the UCR, which collects data on 1st course cancer-related treatment. Variables from the UPDB included family history of breast cancer, family history of cardiovascular disease, and baseline body mass index (BMI). Baseline BMI was calculated from the height and weight provided in the driver's license records one year before the breast cancer diagnosis date. Based on the American Academy of Family Physicians coding guidelines, baseline tobacco users were identified one year before the breast cancer diagnosis based on the International Classification of Diseases ICD-9/ICD-10 diagnosis codes for tobacco cessation and tobacco addiction.[23] The Charlson Comorbidity Index (CCI) was calculated at baseline, from the International Classification of Diseases or ICD-9/ICD-10 diagnosis codes for the year prior to the index date, excluding cancer diagnosis given that the CCI index was based on a cohort of cancer patients. The CCI index score calculation was based on prevalent comorbidities, a year before cancer diagnosis, as a measure of baseline overall health based on previously established algorithm.[24,25] Patients with prevalent diagnosis for the outcome of the interest were excluded, to calculate incidence of the outcomes of interest. For example, patients with previous heart disease were excluded when estimating the HR for incident heart disease after breast cancer diagnosis.

Rurality of residence was classified according to the rural-urban commuting area (RUCA) codes based on the 2010 decennial census and the 2006–2010 American Community Survey (ACS).[26] The RUCA codes classify US census tracts based on standard census measures of urbanization, population density, and daily commuting from the decennial census. The RUCA codes were aggregated into urban (1.0, 1.1, 2.0–2.2, 3.0, 4.1, 5.1, 7.1, 8.1, and 10.1) and rural (4.0–7.0, 7.2–7.4, 8.0, 8.2–8.4, 9.0–9.2, 10.0, 10.2–10.4, and 10.5) group based on suggested C categorization by the Rural Health Research Center's experts.[27] Additionally, median household income for each census tract was available from the US Census Bureau of Economic Analysis.[28] The Yost socioeconomic status index (SES) at the census 2010 tract level was available for Utah from the Surveillance, Epidemiology, and End Results (SEER) registry. The Yost score is a composite index of neighborhood-level census measure of SES, which incorporates average education, occupation, median income, poverty rate,

median housing value, median rent, and unemployment rate.[29] Individual-level education information was available from the UPDB.

Outcome Measures

Outcome data included the following medical records data sources that link with the UPDB: (a) the state ambulatory surgery databases and services databases (SASD), (b) the inpatient hospital claims database from the Utah Department of Health, and (c) the electronic medical record (EMR) data from the University of Utah Health (UUH) and the Intermountain Healthcare (IHC). The UPDB-linked records for approximately 94.9% of patient EMR records were from the IHC, and 54.1% of patient EMRs were from the UUH. For patients encountered in both hospital health systems, the first diagnosis code after cancer diagnosis was considered in the analysis, which avoids the potential of overlapping diagnosis on the same day within each or across the two systems. For instance, some patients used both UUH and IHC, however the earliest diagnosis identified in the medical records was used as the incident diagnosis of the outcomes of interest. The primary outcomes measured were a newly diagnosed cardiovascular disease, mental disorders, diabetes, osteoporosis, cataracts, and hearing impairments identified by available ICD-9 and ICD-10 diagnosis codes from the outcome data. The list of ICD diagnosis codes for each outcome of interest was based on the Chronic Conditions Data Warehouse (CCW),[30] which included 15 adverse health outcomes considered in the analysis that are treatment or cancer diagnosis-related.

Statistical Analysis

All baseline descriptive demographic and clinical characteristics for the breast cancer survivors were stratified by urban and rural residence and compared using the Pearson's chi-square (χ^2). The hazard ratios (HRs) and 99% confidence interval (99% CI)[31] for incident adverse health outcomes in rural compared to urban cancer survivors were estimated using the Cox proportional hazards model from 1 to 5 years and >5 years after the first year from breast cancer diagnosis. Breast cancer survivors with a record of an outcome of interest before the index date were considered prevalent cases, and these cases were excluded from the HR models. The exclusion of prevalent cases in the models allows for calculating incidence. The HR models were stratified to 1 to 5 years and >5 years following the first year from the cancer diagnosis in the interest of investigating the risk of adverse health outcomes following the initial five years after the initial year from cancer diagnosis. The HRs were fit using *PHREG* function. We used the *STRATA* statement on the matched identification number within the *PHREG* function to account for the matching factors in the model. Based on the three properties of a confounder, on the association between the diagnosis of breast cancer and the risk of adverse health outcomes, we considered race and ethnicity as potential confounders because they are risk factors for the outcomes evaluated, associated with rurality and do not act as mediators. BMI, CCI, and socioeconomic status (Yost) may be mediators since rurality may be a predictor of these factors and therefore adjustment for these variables is not needed. The proportional hazards assumption was tested by creating interaction terms as a function of log (time) and the predictor variables. Flexible parametric modeling with restricted splines was used and reported where estimates differed from the original model, indicating a violation of the proportional hazard assumption. The follow-up time was measured from the date of breast cancer diagnosis

(index date), until the earliest occurrence of an event (adverse health outcome) or censoring time (i.e., no outcome, last date of follow-up, or death), whichever occurred first.

Additionally, risk factors for adverse health outcomes of significantly higher risk among rural compared to urban breast cancer survivors were assessed using the Cox proportional hazard models and 95% confidence interval (95% CI). Risk factor models were adjusted for potential confounders, that is, covariates that are risk factors for a given adverse health outcome, associated with the risk factor in question, but unaffected by the risk factor itself (not a mediator). The Cochran's homogeneity test was used to assess HR differences for each risk factor in urban and rural breast cancer survivors.

Using the linear regression model, about 28.7% of the missing education values and 30.2% of the missing BMI values were imputed based on baseline BMI, CCI, race and ethnicity, age at cancer diagnosis, and birth year. Further, to examine the differences between the effects of risk factors by rural and urban residence, we modeled interaction effects. Specifically, we assessed interaction terms of residence with ethnicity, SES, radiotherapy, and surgery (individually) for the outcome of HF. In addition, we modeled one interaction term of residence and HF diagnosis with death as an outcome. P-values for interaction terms were calculated by the likelihood ratio test comparing the model with and without the product term. Crude and adjusted estimates for each component and joint effects were reported.

Statistical analyses were performed in SAS 9.4 (Statistical Analysis System, RRID:SCR_008567, version 9.4; SAS Institute, Inc., Cary, NC, USA). For all statistical analyses, statistical significance was based on two-tailed tests at the *a priori* α level of <0.05 for the assessment of risk factors and <0.01 for the main outcomes of interest. The University of Utah Institutional Review Board (IRB) and the oversight committee for the UPDB, the Resource for Genetic and Epidemiologic Research (RGE), approved this study. Under the IRB regulations, this study received approval for waiver of informed consent. The study was conducted in accordance with the ethical guidelines of the Belmont Report.

Data Availability Statement

Raw data for this study can be accessed by the approval of the Resource for Genetic and Epidemiologic Research Committee (RGE), the oversight committee for the UPDB and IRB.

Results

In total, there were 2,359 (16.7%) rural breast cancer survivors and 11,748 (83.3%) urban breast cancer survivors. Rural breast cancer survivors were more likely to be non-Hispanic White and less likely to have at least a college education (Table 1, $p < 0.0001$). Baseline tobacco use, family history of any cancer, family history of breast cancer, or family history of cardiovascular diseases did not differ between rural and urban survivors. Rural breast cancer survivors were more likely to have had a mastectomy than urban breast cancer survivors (Table 2, $p < 0.0001$). Similarly, a larger proportion of rural breast cancer survivors did not have radiotherapy than urban breast cancer survivors.

For the overall follow-up, rural breast cancer survivors had a 27% higher (HR = 1.27, 95%CI 1.06, 1.53) risk of heart failure (HF) than urban breast cancer survivors, adjusting for the matching factors, race, and ethnicity (Table 3). Breast cancer survivors from rural areas had a 34% lower risk (HR = 0.66, 95%CI 0.56, 0.78) of cataracts, a 19% lower risk (HR = 0.81, 95%CI 0.69, 0.96) of hyperlipidemia, and a 15% lower risk of osteoporosis (HR = 0.85, 95%CI 0.72, 1.00: p = 0.008) than urban breast cancer survivors, adjusting for potential confounders (Table 3).

Within the 5 years of follow-up, rural breast cancer survivors had a 39% (HR = 1.39, 95%CI 1.02, 1.65) higher risk of HF than urban breast cancer survivors, adjusting for confounders (Table 3). Rural breast cancer survivors continued to have lower risks of cataracts and hearing impairments than rural breast cancer survivors after 5-years of follow-up. There was no increase in the risk for other cardiovascular outcomes or mental health outcomes overall, within 5 years and >5 years of follow-up.

Demographic and clinical risk factors were assessed for heart failure because this was the only outcome for which there was an increased risk in rural compared to urban breast cancer survivors. Family history of cardiovascular diseases, family history of breast cancer, lower education attainment (rural only), and higher baseline BMI and CCI were risk factors for HF in rural and urban breast cancer survivors, with similar levels of risk (Table 4). Advanced cancer stage and single-agent chemotherapy treatment were associated with an increased risk for HF following breast cancer diagnosis, however, no heterogeneities were found between rural and urban breast cancer survivors (Table 5). Interaction effects between residence and ethnicity, SES, surgery, and radiotherapy on the risk of HF were not statistically significant (Table 6). An interaction term between residence and HF diagnosis (Table 6, p = 0.024) on the risk of death was statistically significant, indicating differences in risks of death among rural and urban breast cancer survivors, favoring rural breast cancer survivors.

Discussion

In this population-based cohort, we evaluated the burden of cardiovascular disease, diabetes, mental health disorders, cataracts, hearing impairment, and osteoporosis for rural compared to urban breast cancer survivors. Breast cancer survivors in rural compared to urban areas had a higher risk of heart failure (HF) overall and within 1–5 years after the initial year from breast cancer diagnosis. There was no increase in the risk for any other health outcomes evaluated in this study. The risk of cataracts and hearing impairments was lower for rural breast cancer survivors overall, within and >5 years of follow-up. Further, a higher baseline BMI and CCI, family history of CVD, family history of breast cancer, and advanced cancer stage were potential risk factors of incident HF risk, though with similar levels of risk for rural and urban breast cancer survivors.

With respect to demographics, differences in income and ethnicity are consistent with a previous study on disparities in urban and rural breast cancer survivors identified within the SEER database.[11] However, our observation of no difference in baseline BMI and CCI between rural and urban breast cancer survivors in this study was not expected. It is

possible that in Utah, in contrast with other parts of the country, rural and urban breast cancer survivors do not differ greatly for these baseline characteristics. Our study confirmed treatment disparities between rural and urban breast cancer survivors.[32] Radiotherapy in particular is more challenging since daily treatment over several weeks are required,[33,34] and the difficult of traveling a long distance to treatment facilities is a predominant barrier to receiving extended treatments for rural communities. Unlike previous findings,[35] we did not observe any differences for cancer stage between rural and urban breast cancer patients. Utah's overall cancer screening rates are lower than the national average,[36,37] potentially resulting in higher rates of delayed cancer diagnosis than reported in states with a higher percentage of rural women who underwent mammography screening.[38]

The increased HF risk in rural breast cancer survivors in this study may be attributed to more intensive forms of cancer treatments since they are diagnosed at a later stage, which could increase risk of late effects closer to breast cancer diagnosis. However, the increased risk of HF after five years of follow-up was not statistically significant; perhaps because we lacked the statistical power to detect an association. Conversely, due to lower treatment adherence, we hypothesize that rural cancer survivors may experience a lower incidence of treatment-related late effects. Therefore, the increased HF risk observed in this study may in part be due to non-cancer factors, the increased risk of heart failure in women of low-income from rural communities compared with their urban counterparts had been previously reported.[39] These findings highlight the need for primary preventive strategies for rural cancer patients at risk of cardiovascular outcomes, including increased cardiac surveillance and monitoring to help lessen potential barriers to heart health in rural communities.

In terms of HF risk factors, the higher HF risk in single-agent treated breast cancer patients in this study may be due to treatment toxicity leading to treatment discontinuation and patients receiving single rather than multiple needed treatments. However, it may be more plausible that these patients may have received multi-agent treatments but were inaccurately categorized as receiving single instead of multiple treatments. Given that the data on patients who received chemotherapy from the cancer registry may be underrepresented, it is not surprising that we did not observe an association for patients receiving chemotherapy. Similarly, we may have lacked the statistical power needed to detect an association and may not have captured the long-term effects of chemotherapy on the heart.

The risks of other adverse health outcomes evaluated, such as hypertension, diabetes, anxiety, and depression, did not differ between rural and urban breast cancer survivors. Underutilization of healthcare for these health outcomes is likely due to screening barriers in rural areas, or some conditions may not have been severe enough to be captured in our study. Depression and anxiety are of great concern for cancer survivors;[9] however, depending on screening assessment methods or healthcare seeking behaviors, these outcomes may be underdiagnosed among cancer survivors, regardless of residence. It is unclear why rural breast cancer survivors in this study had a lower risk of hyperlipidemia, cataracts, hearing impairment, or osteoporosis. However, due to lower treatment adherence or care management in rural communities, it is possible that rural cancer survivors may have a lower incidence of certain treatment or non-cancer-related effects. To further investigate the effects

of breast cancer treatment or cancer diagnosis on rural breast cancer survivors, future studies using a general population without cancer as a comparison group are needed.

The major strength of this study is that it is the first study to comprehensively assess adverse health outcomes through prolonged follow-up of a relatively large sample of rural breast cancer survivors. Further, all diagnoses are based on electronic medical and ambulatory discharge records from large state regional healthcare providers in the state and are not subject to recall bias, which is problematic for studies based on self-reported outcomes. Similarly, while electronic medical records may not capture less severe diagnoses, medical records allow for the inclusion of a wide range of available ICD diagnosis codes for the identification of evaluated adverse health outcomes.

There are limitations to consider for this study. Although our sample included approximately 4.6% rural and 9.9% urban Hispanic breast cancer survivors, it is unlikely that our findings can be generalizable to more diverse rural regions of the US. Similarly, Utah's low alcohol drinking and cigarette smoking rates compared to the rest of the country[40] may contribute to a healthier cohort of breast cancer survivors, potentially resulting in lower comorbidity risk estimates compared to other breast cancer cohorts. In the first few years following a cancer diagnosis, cancer survivors undergo increased medical surveillance, including more frequent follow-up visits and medical screening. However, breast cancer survivors in rural communities may receive fewer follow-up visits in the early years following a cancer diagnosis, which may minimize the frequency of outcomes evaluated. Nevertheless, there was a higher risk of HF in the first 5 years of follow-up among rural breast cancer survivors. Given the number of patients with ER positive breast cancer, endocrine therapy usage is likely underreported in the overall study sample. These missing data are likely to bias the results towards the null, regardless of residency.

In conclusion, we observed an increased risk of heart failure among rural compared to urban breast cancer survivors. Future studies are needed to investigate preventive approaches to identify patients at high risk of cardiovascular outcomes for whom preventive strategies are warranted and can be implemented in rural areas to reduce the comorbidity burden among rural breast cancer survivors. Although other adverse health outcomes did not differ for rural and urban breast cancer survivors in this study, investigating these outcomes remains essential for understanding the comorbidity burden across rural populations in the United States.

Acknowledgements

This work was supported by grants from the NIH (R01 CA244326, R21 CA185811, R03 CA159357, M. Hashibe, PI), the Huntsman Cancer Institute, and the Cancer Control and Population Sciences Program (HCI Cancer Center Support Grant P30CA042014). This research was supported by the Utah Cancer Registry, which is funded by the National Cancer Institute's SEER Program, Contract No. HHSN261201800016I, the U.S. Center for Disease Control and Prevention's National Program of Cancer Registries, Cooperative Agreement No. NU58DP007131-01, with additional support from the University of Utah and Huntsman Cancer Foundation. Partial support for all datasets within the Utah Population Database is provided by the University of Utah, Huntsman Cancer Institute and the Huntsman Cancer Institute Cancer Center Support grant, P30CA042014 from the National Cancer Institute. The computational resources used were partially funded by the NIH Shared Instrumentation Grant 1S10OD021644-01A1.

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TABLE 1.

Baseline Characteristics Among Breast Cancer Survivors Diagnosed in 1997–2017, by Rural and Urban Residence in Utah[a]

Characteristics: No. (%)	Rural (n = 2,359)		Urban (n = 11,748)		*P* [b]
Ethnicity					
Non-Hispanic White	2,209	(93.6)	10,171	(86.5)	
Hispanic	115	(4.9)	1,218	(10.4)	
Other[c]	35	(1.5)	359	(3.1)	*<0.0001*
Maximum follow-up time (y)					
1–5	804	(34.1)	3,753	(31.9)	
6–10	718	(30.4)	3,674	(31.3)	
11–15	463	(19.6)	2,360	(20.1)	
>15	374	(15.9)	1,961	(16.7)	*0.2347*
Baseline BMI (kg/m^2) [d]					
<18.5	46	(2.0)	181	(1.5)	
18.5–24.9	1,027	(43.5)	5,199	(44.3)	
25.0–29.9	729	(30.9)	3,761	(32.0)	
≥30.0	557	(23.6)	2,607	(22.2)	*0.1866*
Baseline CCI					
0	1,445	(61.2)	7,089	(60.3)	
1	464	(19.7)	2,521	(21.5)	
≥2	450	(19.1)	2,138	(18.2)	*0.1308*
Baseline tobacco use					
No	2,207	(93.6)	10,967	(93.4)	
Yes	152	(6.4)	781	(6.6)	*0.7153*
Family history of any cancer [e]					
No	979	(41.5)	4,897	(41.7)	
Yes	1,380	(58.5)	6,851	(58.3)	*0.8693*
Family history of breast cancer [e]					
No	1,341	(56.8)	6,846	(58.3)	
Yes	1,018	(43.2)	4,902	(41.7)	*0.1998*
Family history of CVDs [e]					
No	920	(39.0)	4,550	(38.7)	
Yes	1,439	(61.0)	7,198	(61.3)	*0.8063*
Education[d]					
<high school	386	(16.4)	1,689	(14.4)	
High school degree	836	(35.4)	3,842	(32.7)	
Some college	686	(29.1)	3,494	(30.0)	
College degree	275	(11.7)	1,616	(13.7)	
>college	176	(7.4)	1,107	(9.2)	*<0.0001*
Household median income (census tract)					

Characteristics: No. (%)	Rural (n = 2,359)		Urban (n = 11,748)		*P* [b]
<$50,000	920	(39.0)	5,476	(46.6)	
$50,000 to <$60,000	1,082	(45.9)	2,553	(21.7)	
$60,000 to <$70,000	248	(10.5)	1,109	(9.5)	
≥$70,000	109	(4.6)	2,610	(22.2)	*<0.0001*
Yost SES index (census tract, quintile)					
Q1 (lowest)[f]	755	(32.0)	1,528	(12.9)	
Q2	829	(35.1)	4,663	(39.7)	
Q3	424	(18.0)	2,159	(18.3)	
Q4	295	(12.5)	1,522	(13.0)	
Q5	56	(2.4)	1,876	(16.0)	*<0.0001*

Abbreviations: BMI, body mass index; SES, socioeconomic status; CCI, Charlson Comorbidity Index; CVDs, cardiovascular diseases.

[a] Urban breast cancer survivors were matched to rural breast cancer survivors on diagnosis year and age at cancer diagnosis.

[b] Two-sided Pearson's chi-square was used to compare the proportions between rural and urban breast cancer survivors.

[c] Other races included: African American, American Indian/Alaskan, Hawaiian and Other Pacific Islander, Native American, and Asian.

[d] Approximately 28.7% of missing education and 30.2% of missing BMI values were imputed.

[e] In first-, second-, and third-degree relatives.

[f] Values with ≤11 observations were compressed in accordance with the data confidentiality policy (unknown values compressed with first quartile).

TABLE 2.

Clinical and Treatment Characteristics Among Breast Cancer Survivors Diagnosed in 1997–2017, by Rural and Urban Residence in Utah[a]

Characteristics: No. (%)	Rural (n = 2,359)		Urban (n = 11,748)		*p* [b]
Age at cancer diagnosis (y)					
24–40	164	(7.0)	797	(7.0)	
41–50	416	(17.6)	2,093	(17.6)	
51–60	567	(24.0)	2,824	(24.0)	
61–70	594	(25.2)	2,984	(25.4)	
71–97	618	(26.2)	3,050	(26.0)	
AJCC stage [c]					
I	1,064	(45.1)	5,373	(45.7)	
II	871	(36.9)	4,456	(37.9)	
III	256	(10.9)	1,264	(10.8)	
IV	89	(3.8)	376	(3.2)	*0.4767*
Histology					
Ductal	1,784	(75.6)	8,572	(73.0)	
Lobular	372	(15.8)	2,250	(19.1)	
Other	203	(8.6)	926	(7.9)	*0.0001*
Estrogen-receptor [c]					
Positive	1,846	(78.3)	9,238	(78.6)	
Negative	380	(16.1)	2,022	(17.2)	*0.3179*
Progesterone-receptor [c]					
Positive	1,606	(68.1)	8,091	(68.9)	
Negative	605	(25.6)	3,063	(26.1)	*0.9250*
HER2 status (>2010)[c, d]					
Positive	146	(6.2)	752	(6.4)	
Negative	832	(35.3)	4,065	(34.6)	*0.5905*
Endocrine therapy					
No	1,332	(56.5)	6,897	(58.7)	
Yes	1,027	(43.5)	4,851	(41.3)	*0.0437*
Surgery					
None	91	(3.9)	392	(3.3)	
Lumpectomy[e]	1,148	(48.6)	6,405	(54.5)	
Mastectomy	1,120	(47.5)	4,951	(42.2)	*<0.0001*
Chemotherapy					
None	1,364	(57.7)	6,930	(59.0)	
Single-agent	830	(35.2)	4,029	(34.3)	
Multiple-agents	53	(2.3)	245	(2.1)	
Number of agents unknown	112	(4.8)	544	(4.6)	*0.7515*
Radiotherapy					

Characteristics: No. (%)	Rural (n = 2,359)		Urban (n = 11,748)		*P* [b]
None	1,129	(47.9)	5,072	(43.2)	
External beam	1,160	(49.1)	6,288	(53.5)	
Radioactive implant	52	(2.2)	331	(2.8)	
Radioisotopes, combination, or unspecified[f]	18	(0.8)	57	(0.5)	*<0.0001*

Abbreviations: AJCC, American Joint Committee on Cancer; HER2, human epidermal growth factor receptor.

[a] Urban survivors were matched to rural survivors on diagnosis year and age at cancer diagnosis.

[b] Two-sided Pearson's chi-square was used to compare the proportions between rural and urban breast cancer survivors.

[c] There were unknown values for rural and urban breast cancer survivors for stage (79 (3.3%) and 279 (2.4%)), and borderline values for ER (133 (5.6%) and 488 (4.2%)), PR (148 (6.3%) and 594 (5.0%)), and HER2 status (1,381 (58.5%) and 6,931 (59.0%)).

[d] The HER2 breast cancer subtype information was unavailable in the Utah Cancer Registry until 2010.

[e] Values with ≤11 observations were suppressed in accordance with the data confidentiality policy. The "*local tumor destruction*" category for surgery was combined with "*lumpectomy*" to avoid ≤11 observations per cell count, as per data confidentiality policy.

[f] The radiotherapy combination included: beam radiotherapy with a radioactive implant or radioisotopes.

Table 3.

Adverse Health Outcomes Overall, at 1–5 Years and >5 Years After the Initial Year From Breast Cancer Diagnosis in Rural Compared to Urban (reference) Breast Cancer Survivors Diagnosed in 1997–2017 [a]

	Overall						1 to 5 years						>5 years					
	Rural N = 2,359		Urban N = 11,748				Rural N = 2,359		Urban N = 11,748				Rural N = 1,386		Urban N = 7,145			
	No.	(%)	No.	(%)	HR *b*	(99%CI)	No.	(%)	No.	(%)	HR *b*	(99%CI)	No.	(%)	No.	(%)	HR *b*	(99%CI)
Anemia	444	(24.1)	1,916	(26.8)	0.93	(0.80, 1.07)	256	(13.9)	1,063	(14.9)	0.94	(0.78, 1.14)	195	(19.5)	666	(21.9)	0.91	(0.73, 1.15)
Anxiety disorders	399	(21.5)	1,552	(20.8)	1.12	(0.95, 1.31)	227	(12.2)	782	(10.5)	1.18	(0.97, 1.45)	172	(15.3)	812	(20.8)	1.02	(0.80, 1.29)
Atrial fibrillation and flutter	245	(11.1)	1,010	(9.8)	1.10	(0.90, 1.34)	97	(4.4)	445	(4.3)	0.96	(0.71, 1.29)	156	(15.0)	463	(28.0)	1.20	(0.93, 1.57)
Cataracts	333	(16.0)	1,972	(21.8)	**0.66**	**(0.56, 0.78)**	165	(7.9)	949	(10.5)	**0.67**	**(0.54, 0.85)**	149	(15.0)	521	(18.2)	**0.63**	**(0.50, 0.80)**
Depression, bipolar, other mood disorders	373	(20.6)	1,501	(21.8)	0.96	(0.82, 1.13)	230	(12.7)	844	(12.3)	1.01	(0.81, 1.25)	161	(13.0)	504	(10.8)	0.84	(0.65, 1.09)
Diabetes	258	(13.1)	1,075	(13.0)	1.05	(0.87, 1.28)	142	(7.2)	561	(6.8)	1.10	(0.85, 1.42)	215	(26.5)	616	(28.5)	0.98	(0.75, 1.30)
Hearing impairments	119	(7.7)	839	(5.2)	**0.68**	**(0.52, 0.90)**	58	(2.5)	364	(3.3)	0.77	(0.53, 1.12)	198	(15.9)	767	(16.6)	**0.62**	**(0.43, 0.91)**
Heart failure and non-ischemic heart disease	311	(14.6)	1,156	(11.6)	**1.27**	**(1.06, 1.53)**	159	(7.4)	560	(5.6)	**1.39**	**(1.02, 1.65)**	181	(30.1)	441	(27.1)	1.23	(0.95, 1.59)
Hip or pelvic fracture	125	(5.4)	553	(4.9)	1.18	(0.89, 1.57)	63	(2.7)	277	(2.4)	1.15	(0.79, 1.68)	63	(4.7)	202	(3.8)	1.28	(0.95, 1.93)
Hyperlipidemia	391	(25.2)	1,645	(29.6)	**0.81**	**(0.69, 0.96)**	198	(12.7)	860	(15.5)	**0.78**	**(0.63, 0.97)**	138	(11.5)	494	(11.4)	0.90	(0.71, 1.13)
Hypertension	375	(31.7)	1,171	(29.6)	1.03	(0.87, 1.23)	193	(16.3)	595	(15.0)	1.02	(0.81, 1.28)	168	(15.0)	612	(16.5)	1.07	(0.82, 1.38)
Hypothyroidism	293	(16.2)	1,088	(15.8)	1.06	(0.88, 1.28)	162	(9.0)	623	(9.1)	1.03	(0.81, 1.30)	144	(14.8)	368	(12.7)	1.12	(0.84, 1.48)
Ischemic heart disease	254	(12.1)	1,173	(12.4)	0.95	(0.78, 1.15)	121	(5.8)	568	(6.0)	0.91	(0.70, 1.20)	98	(7.6)	382	(7.7)	1.01	(0.77, 1.32)
Osteoporosis	355	(17.0)	1,773	(19.4)	**0.85**	**(0.72, 1.00)**	198	(9.5)	991	(10.9)	0.84	(0.69, 1.04)	185	(17.5)	596	(18.0)	0.89	(0.69, 1.13)

	Overall						1 to 5 years						>5 years					
	Rural N = 2,359		Urban N = 11,748				Rural N = 2,359		Urban N = 11,748				Rural N = 1,386		Urban N = 7,145			
	No.	(%)	No.	(%)	HR *b*	(99%CI)	No.	(%)	No.	(%)	HR *b*	(99%CI)	No.	(%)	No.	(%)	HR *b*	(99%CI)
Stroke or transient ischemic attack	188	(8.4)	880	(8.3)	0.98	(0.78, 1.22)	93	(4.1)	417	(3.9)	1.02	(0.76, 1.39)	63	(4.8)	368	(7.4)	0.93	(0.68, 1.27)

Abbreviations: HR, hazard ratio; CI, confidence interval.

[a]The number and percent for each outcome excluded prevalent cases. Urban breast cancer survivors were matched to rural breast cancer survivors on cancer diagnosis year and age at cancer diagnosis.

[b]Models were adjusted for the matching factors, race, and ethnicity.

[c]Flexible model was used where the proportional hazards assumption was violated for 1 to 5 years for Depression, bipolar, and other mood disorders (HR = 1.00, 99%CI 0.83, 1.21); for >5 years for Hyperlipidemia (HR = 0.87, 99%CI 0.72, 1.06), Stroke or transient ischemic attack (HR = 1.03, 99%CI 0.77, 1.37), and Anxiety disorders (HR = 0.99, 99%CI 0.81, 1.22).

TABLE 4.

Demographic Baseline Risk Factors for Heart Failure After Breast Cancer Diagnosis for Urban and Rural Residence in Utah (1997–2017)

	Rural		Urban		
	HR	**(95% CI)**	**HR**	**(95% CI)**	***P*** [a]
Ethnicity [b]					
Non-Hispanic White					
Hispanic	1.34	(0.83, 2.16)	0.92	(0.76, 1.10)	*0.151*
Other	0.57	(0.18, 1.77)	**0.50**	**(0.32, 0.79)**	*0.834*
Baseline BMI (kg/m^2) [c]					
<18.5	1.01	(0.37, 2.75)	0.69	(0.37, 1.30)	*0.528*
18.5–24.9		Ref		Ref	
25.0–29.9	1.24	(0.95, 1.61)	**1.16**	**(1.02, 1.32)**	*0.656*
≥30.0	**1.48**	**(1.11, 1.98)**	**1.63**	**(1.42, 1.87)**	*0.555*
Baseline CCI [c]					
0		Ref		Ref	
1	1.15	(0.86, 1.53)	**1.45**	**(1.27, 1.66)**	*0.286*
≥2	**1.76**	**(1.28, 2.41)**	**2.05**	**(1.77, 2.38)**	*0.392*
Baseline tobacco use [d]					
No		Ref		Ref	
Yes	1.37	(0.80, 2.33)	**1.31**	**(1.02, 1.68)**	*0.882*
Family history of CVDs [e]					
No		Ref		Ref	
Yes	**1.29**	**(1.00, 1.65)**	**1.23**	**(1.09, 1.39)**	*0.737*
Family history of breast cancer [f]					
No		Ref		Ref	
Yes	**1.25**	**(1.00, 1.57)**	**1.16**	**(1.04, 1.29)**	*0.558*
Education [f]					
<high school	**1.37**	**(1.03, 1.82)**	1.06	(0.92, 1.24)	*0.118*
High school degree		Ref		Ref	
Some college	0.93	(0.69, 1.26)	0.99	(0.87, 1.15)	*0.712*
College degree	0.75	(0.47, 1.19)	**0.80**	**(0.65, 0.99)**	*0.804*
>college	0.56	(0.29, 1.08)	0.83	(0.64, 1.05)	*0.272*
Yost SES index (census tract, quintile) [f]					
Q1 (lowest)	1.09	(0.84, 1.43)	**1.20**	**(1.02, 1.43)**	*0.550*
Q2		Ref		Ref	
Q3	1.04	(0.74, 1.48)	0.95	(0.81, 1.11)	*0.641*
Q4	0.74	(0.48, 1.14)	0.93	(0.78, 1.11)	*0.338*
Q5	1.27	(0.40, 4.05)	0.87	(0.73, 1.04)	*0.527*

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval; CVDs, cardiovascular diseases; Ref, reference.

[a] Cochran's Q statistic was used to test for the heterogeneity in risk estimates in rural and urban breast cancer survivors at the p-value of 0.05 (>0.05 indicates no heterogeneity).

[b] Models were unadjusted.

[c] Models were adjusted for race, ethnicity, tobacco use, education, and age at cancer diagnosis.

[d] Models were adjusted for race, ethnicity, CCI, education, and year and age at cancer diagnosis.

[e] Models were adjusted for race, ethnicity, CCI, BMI, tobacco use, and age at cancer diagnosis.

[f] Models were adjusted for race and ethnicity.

TABLE 5.

Clinical Risk Factors for Heart Failure at ≥1 Year Following Breast Cancer Diagnosis by Urban and Rural Residence in Utah (1997–2017)

	Rural		Urban		
	HR	**(95% CI)**	**HR**	**(95% CI)**	***P*** [a]
AJCC stage [b]					
I		Ref		Ref	
II	1.24	(0.96, 1.59)	**1.26**	**(1.12, 1.42)**	*0.910*
III	**2.08**	**(1.41, 3.07)**	**1.86**	**(1.53, 2.27)**	*0.615*
IV	**2.58**	**(1.38, 4.82)**	**1.96**	**(1.39, 2.76)**	*0.450*
Estrogen-receptor [c]					
Positive		Ref		Ref	
Negative	1.33	(0.97, 1.82)	**1.17**	**(1.01, 1.36)**	*0.468*
Progesterone-receptor [c]					
Positive		Ref		Ref	
Negative	1.18	(0.90, 1.55)	1.10	(0.97, 1.25)	*0.646*
HER2 status (>2010) [c]					
Negative		Ref		Ref	
Positive	1.56	(0.78, 3.12)	**1.55**	**(1.10, 2.16)**	*1.000*
Endocrine therapy [d]					
No		Ref		Ref	
Yes	1.01	(0.78, 1.30)	0.96	(0.85, 1.10)	*0.728*
Surgery [d]					
None		Ref		Ref	
Lumpectomy	0.54	(0.21, 1.40)	0.67	(0.40, 1.10)	*0.694*
Mastectomy	0.57	(0.22, 1.50)	0.87	(0.53, 1.43)	*0.443*
Chemotherapy [d]					
None		Ref		Ref	
Single-agent	**2.51**	**(1.08, 5.81)**	1.50	(1.00, 2.26)	*0.280*
Multiple-agents	1.01	(0.74, 1.40)	0.92	(0.79, 1.08)	*0.606*
Number of agents unknown	1.09	(0.60, 1.98)	1.12	(0.86, 1.47)	*0.935*
Radiotherapy [d]					
None		Ref		Ref	
External beam	0.91	(0.73, 1.19)	**0.85**	**(0.76, 0.96)**	*0.515*
Radioactive implant	0.93	(0.34, 2.57)	0.94	(0.63, 1.39)	*0.940*
Radioisotopes, combination, or unspecified	0.83	(0.11, 6.14)	0.99	(0.41, 2.40)	*0.915*

Abbreviations: AJCC, American Joint Committee on Cancer; HR, hazard ratio; CI, confidence interval; Ref, reference.

[a]Cochran's Q statistic was used to test for the heterogeneity in risk estimates in rural and urban breast cancer survivors at $p < 0.05$ (>0.05 indicates no heterogeneity).

[b]Model was adjusted for BMI, CCI, race, ethnicity, tobacco use, education, age at cancer diagnosis, and year at cancer diagnosis.

[c] Models were adjusted for BMI, CCI, race, ethnicity, tobacco use, and age at cancer diagnosis. HER2 for cancer subtype characterization was unavailable in the Utah Cancer Registry until 2010.

[d] Models were adjusted for BMI, CCI, race, ethnicity, education, tumor grade, cancer stage, age at cancer diagnosis, and year at cancer diagnosis.

TABLE 6.

Component and Joint Effects to Evaluate Interactions, Between Rural and Urban Residence in Utah and Selected Risk Factors on The Outcomes of Death and Heart Failure Among Breast Cancer Survivors (1997–2017)

	Crude HR	(95% CI)	*P* [a]	Adjusted HR	(95% CI)	*P* [a]
Outcome: heart failure						
Ethnicity[b]						
Urban: White		Ref				
Urban: Other	1.46	(1.26, 1.70)				
Rural: White	0.83	(0.67, 1.03)				
Rural: Other (combined)[f]	0.97	(0.52, 1.80)	*0.146*			
Socioeconomic status (SES)[c]						
Urban: SES (Q≥4)		Reference		Reference		
Urban: SES (Q<4)	1.14	(0.99, 1.31)	1.13	(0.96, 1.32)		
Rural: SES (Q≥4)	1.08	(0.71, 1.64)	1.11	(0.70, 1.77)		
Rural: SES (Q<4, combined)[f]	**1.39**	**(1.14, 1.68)**	*0.613*	**1.37**	**(1.13, 1.66)**	*0.599*
Surgery[d]						
Urban: without surgery		Reference		Reference		
Urban: with surgery	0.64	(0.38, 1.08)	1.31	(0.52, 3.28)		
Rural: without surgery	1.45	(0.53, 3.96)	3.57	(0.58, 22.0)		
Rural: with surgery (combined)[f]	0.81	(0.48, 1.37)	*0.772*	1.54	(0.61, 3.89)	*0.237*
Radiotherapy[d]						
Urban: without radiotherapy		Reference		Reference		
Urban: with radiotherapy	0.89	(0.78, 1.03)	0.86	(0.75, 1.01)		
Rural: without radiotherapy	**1.25**	**(1.02, 1.54)**	1.14	(0.91, 1.42)		
Rural: with radiotherapy (combined)[f]	1.12	(0.90, 1.39)	*0.987*	1.11	(0.88, 1.40)	*0.509*
Cemotherapy[d]						
Urban: without chemotherapy		Reference		Reference		
Urban: with chemotherapy	**1.37**	**(1.17, 1.60)**	**1.15**	**(0.96, 1.38)**		
Rural: without chemotherapy	**1.25**	**(1.04, 1.49)**	1.21	(0.99, 1.48)		
Rural: with chemotherapy (combined)[f]	**1.72**	**(1.35, 2.19)**	*0.967*	**1.31**	(0.99, 1.75)	*0.739*
Outcome: death [e]						
Urban: without heart failure		Reference			Reference	
Urban: with heart failure	**1.22**	**(1.08, 1.37)**		**1.15**	**(1.02, 1.30)**	
Rural: without heart failure	**1.16**	**(1.03, 1.30)**		1.09	(0.97, 1.23)	
Rural: with heart failure (combined)[f]	1.05	(0.86, 1.26)	*0.013*	0.94	(0.78, 1.14)	*0.024*

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; HR, hazard ratio; CI, confidence interval.

[a] Likelihood-ratio test for interaction terms at $p < 0.05$. Urban breast cancer survivors were matched to rural breast cancer survivors on diagnosis year and age at cancer diagnosis.

[b] Unadjusted.

[c] Models were adjusted for BMI, CCI, race, ethnicity, and smoking status.

[d] Models were adjusted for BMI, CCI, race, ethnicity, education, tumor grade, and cancer stage.

[e] Models were adjusted for BMI, CCI, race, ethnicity, tobacco use, socioeconomic status, and cancer treatment.

[f] Hypothesized most risk.