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Rural–Urban Residence and Stage at Breast Cancer Diagnosis Among Postmenopausal Women: The Women's Health Initiative

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Abstract

Background: Although social exposures have complex and dynamic relationships and interactions, the existing literature on the impact of rural–urban residence on stage at breast cancer diagnosis does not examine heterogeneity of effect. We examined the joint effect of social support, social relationship strain, and rural–urban residence on stage at breast cancer diagnosis.

Methods: Using data from the Women's Health Initiative (WHI) ($n = 161{,}808$), we describe the distribution of social, behavioral, and clinical factors by rural–urban residence among postmenopausal women with incident breast cancer ($n = 7{,}120$). We used rural–urban commuting area (RUCA) codes to categorize baseline residential addresses as urban, large rural city/town, or small rural town, and the surveillance, epidemiology, and end results staging system to categorize breast cancer stage at diagnosis (dichotomized as early or late). We then used univariable and multivariable logistic regression to estimate odds ratios (ORs) and associated 95% confidence intervals (95% CI) for the relationship between rural–urban residence and stage at breast cancer diagnosis. We included separate interaction terms between rural–urban residence and social strain and social support to test for statistical interaction.

Results: Of the social, behavioral, and clinical factors we examined, only younger age at WHI enrollment screening was significantly associated with late stage at breast cancer diagnosis ($p = 0.003$). Contrary to our hypothesis, rural–urban residence was not significantly associated with stage at breast cancer diagnosis among postmenopausal women ([adjusted OR, 95% CI] for urban compared with small town: 1.08 [0.76–1.53]; large town compared with small town: 1.16 [0.74–1.84]; and urban compared with large town: 0.93 [0.68–1.26]).The associations did not vary by social support or social strain (p for interaction between RUCA and social strain and social support, respectively: 0.99 and 0.17).

Conclusions: Future studies should examine other potential effect modifiers to identify novel factors predictive or protective for late stage at breast cancer diagnosis associated with rural–urban residence.

Keywords: stage at breast cancer diagnosis, rural–urban, postmenopausal, social strain and support

Introduction

Breast cancer is a serious public health issue, especially for older women. Stage at cancer diagnosis is directly related to cancer screening behaviors and predicts both survival and quality of life after cancer.[1,2] Access to screening mammography increases the likelihood of early detection and successful breast cancer treatment. However, factors such as access to screening, various health behaviors, and quality of care are highly patterned by where people live.[3,4] Rural residents tend to be older, have lower socioeconomic position, are more likely to smoke and be obese, lack health

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insurance coverage, and have reduced access and utilization of cancer screening than residents of urban areas.[5,6] All of these factors contribute to late stage at breast cancer diagnosis.[7] Rural residents comprise 20% of the U.S. population, and cancer disparities in this group can have a significant impact on the overall health of the nation.[6]

Some studies have documented a ''rural penalty,'' in which persistently higher cancer incidence and mortality rates occur in rural versus urban areas.[5,8,9] Others have found evidence of an urban disadvantage in terms of cancer stage at diagnosis.[10] The authors of the latter study suggested that their findings may be a function of the unique geographic distribution of vulnerable residents in urban (Chicago, IL) compared with more rural areas.[10] More research is needed to understand the unique context for life and risk of cancer across the rural–urban continuum.[11]

The rural–urban commuting area (RUCA) taxonomy[12,13] is the recommended and most commonly used method for categorizing rural versus urban census tracts, especially for cancer researchers, given that it takes into account population density, travel distance, and commuting flows.[14,15] The existing literature on the association between rural–urban residence (using the RUCA taxonomy) and stage at breast cancer diagnosis is small and suggests no significant direct effect.[2,16] However, social exposures such as the residential environment likely interact with and have complicated and dynamic relationships with other social factors.[17,18] Said differently, the impact of rural–urban residence on stage at breast cancer diagnosis might be exacerbated or buffered by other social factors.

Social support (the useful aspects of relationships)[19] and social strain (negative aspects of social relationships or nonsupportive social ties)[20] can positively affect cancer screening behaviors such as repeated mammography, as well as clinical- and self-breast examinations.[21,22] Furthermore, a sizeable literature has identified social support as an important protective factor for breast cancer development and progression,[23–26] and as a predictor of physical activity and health status among rural breast cancer survivors.[27] In contrast, strained relationships have been associated with earlier mortality,[28,29] and socially isolated women have been shown to have higher breast cancer mortality than their socially integrated counterparts.[30] Given this, it is plausible that the association between rural–urban residence and stage at breast cancer diagnosis is buffered by social support and/or exacerbated by social strain, but no studies have tested these hypotheses.

To build upon the existing literature, we examined whether rural–urban residence was associated with stage at breast cancer diagnosis among a large well-defined racially/ethnically diverse cohort of postmenopausal women, with adjudicated incident cancer outcomes, from the Women's Health Initiative (WHI) observational study and clinical trials. We also tested whether social strain and social support modified the relationship between rural–urban residence and stage at breast cancer diagnosis. We hypothesized that the association between rural–urban residence and stage at diagnosis would be exacerbated by social strain and buffered by social support.

Materials and Methods

Study population

The WHI included 161,808 racial/ethnically diverse postmenopausal women, with 68,132 enrolled in dietary modification (DM), calcium /vitamin D, and hormone therapy (HT) clinical trials, and 93,676 in the observational study (OS). Enrollment occurred from 1993 to 1998, and included women from across 40 U.S. clinical centers, from 24 states and the District of Columbia. Details of the WHI have been published.[31–33] Women were eligible to participate in the WHI if they were (1) between 50 and 79 years old, (2) postmenopausal, (3) willing to give informed consent, and (4) expected to survive and not relocate for the next 3 years.

From the original cohort of 161,808 patients, our analytic sample included $n=7,120$ study participants who were diagnosed with incident breast cancer between 1995 and 2014. Updates on incident breast cancers were reported semiannually for the clinical trials and annually for the observational study, and all cancers were confirmed by trained physician adjudicators after review of the medical records. Study participants' estimated probability of developing breast cancer was quantified with the Gail risk assessment tool that utilized age, history of benign breast disease, age at menarche, age at first live birth, race/ethnicity, and number of relatives with breast cancer.[34]

Rural–urban classification

RUCA codes are used to classify all U.S. census tracts into 1 of 10 main categories based on the rural–urban core and the extent of commuting, as well as 33 subcategories based on secondary commuting flows.[35] WHI participant addresses were geocoded as previously described,[36,37] and their corresponding census tracts were assigned RUCA codes based on a reference document provided by the USDA.[35] An aggregation scheme was used to categorize codes into one of four classes: (1) urban or ''metropolitan'' area, (2) large rural city/town or ''micropolitan,'' (3) small rural town, and (4) isolated small rural town. Given the sparsity of WHI participants living in isolated small rural communities, we combined the small rural ($n=113$) and isolated small rural town ($n=99$) categories for our analysis. Considering the possibility of multiple RUCA codes (the RUCA taxonomy is not consistent across census years)[35], we assigned each participant a RUCA code using the version of RUCA closest to the date at which her home address was collected. For our analysis, we used the RUCA codes based on the year 2000 census, since this time point is closest to the midpoint of WHI data collection (1995–2014) and allows us to include the largest number of WHI participants and thus the largest number of incident breast cancer cases in the analysis.

Stage at breast cancer diagnosis

Stage at breast cancer diagnosis was coded based on the surveillance, epidemiology, and end results (SEER) criteria.[38] There were 6,782 (95%) women who had centrally adjudicated incident cancers and SEER-coded data on stage at breast cancer diagnosis, as well as an appropriate address, closest to the time they were diagnosed, for geocoding.

Covariates

A priori, we identified several potential confounding variables based on clinical relevance. Self-reported age at breast cancer screening (50–59, 60–69, 70–79, and 80+), education (less than high school, high school diploma or general equivalency diploma (GED), some college, and college graduate), health insurance (yes/no), and clinical trials

Table 1. Characteristics of Women with Incident Breast Cancer by Rural–Urban Residence at the Time of Diagnosis; Women's Health Initiative (N=7,120), 1993–2014

Characteristics	*Total sample* N=*7,120 (%)*	*Rural–urban category*		
		Urban N=*6,643 (%)*	*Large rural* N=*265 (%)*	*Small rural* N=*212 (%)*
Sociodemographic/psychosocial				
Age (years)				
50–59	2,137 (30)	1,989 (30)	75 (28)	73 (34)
60–69	3,336 (47)	3,109 (47)	128 (48)	99 (47)
70–79	1,647 (23)	1,545 (23)	62 (23)	40 (19)
Race/ethnicity				
White	6,192 (87)	5,732 (86)	257 (97)	203 (96)
Black	508 (7)	495 (7)	4 (2)	9 (4)
Other	403 (6)	399 (6)	4 (2)	0
Education				
None/some HS	266 (4)	241 (4)	11 (4)	14 (7)
HS/GED	1,094 (15)	988 (15)	58 (22)	48 (23)
>HS	5,700 (80)	5,359 (81)	192 (72)	149 (70)
Any insurance				
No	221 (3)	201 (3)	11 (4)	9 (4)
Yes	6,843 (96)	6,389 (96)	252 (95)	202 (95)
Social strain				
Median (IQR)	6 (4,8)	6 (4,8)	6 (4,8)	6 (4,8)
(min, max)	(4,20)	(4,20)	(4,16)	(4,16)
Social strain				
Low (≤5)	3,047 (43)	2,846 (43)	117 (44)	84 (40)
High (>5)	3,935 (55)	3,667 (55)	145 (55)	123 (58)
Social support				
Median (IQR)	37 (32,43)	37 (32,42)	37 (34,53)	38 (32,44)
(min, max)	(9,45)	(9,45)	(12,45)	(17,45)
Social support				
Low (≤37)	3,553 (50)	3,321 (50)	135 (51)	97 (46)
High (>37)	3,404 (48)	3,163 (48)	129 (49)	112 (53)
Health behaviors/history				
Family history of breast cancer				
No	5,083 (71)	4,768 (72)	171 (65)	144 (68)
Yes	1,656 (23)	1,527 (23)	72 (27)	57 (27)
Gail risk				
<1.67%	3,526 (50)	3,290 (50)	116 (44)	120 (57)
≥1.67%	3,594 (50)	3,353 (50)	149 (56)	92 (43)
Mammogram in past 2 years				
Yes	6,065 (85)	5,678 (85)	215 (81)	172 (81)
No	861 (12)	778 (12)	44 (17)	39 (18)
WHI trial participation				
No	2,853 (40)	2,660 (40)	107 (40)	86 (41)
Yes	4,267 (60)	3,983 (60)	158 (60)	126 (59)
WHI study type				
OS	4,267 (60)	3,983 (60)	158 (60)	126 (59)
E-alone	228 (4)	205 (3)	9 (3)	14 (7)
E+P trial	436 (6)	391 (6)	27 (10)	18 (8)
DM	1,883 (26)	1782 (27)	59 (22)	42 (20)
E-alone/E+P trial + DM	306 (4)	282 (4)	12 (5)	12 (6)
Alcohol				
Nondrinker	667 (9)	578 (9)	46 (17)	43 (20)
Former drinker	1,208 (17)	1,125 (17)	44 (17)	39 (18)
Current drinker	5,188 (73)	4,885 (74)	175 (66)	128 (60)
Smoking				
Never smoker	3,432 (48)	3,156 (48)	147 (55)	129 (61)
Past smoker	3,149 (44)	2,981 (45)	104 (39)	64 (30)
Current smoker	443 (6)	416 (6)	10 (4)	17 (8)
Self-rated health				
Excellent/very good	4,245 (60)	3,988 (60)	150 (57)	107 (50)
Good	2,264 (32)	2,088 (31)	93 (35)	83 (39)
Fair/poor	575 (8)	533 (8)	22 (8)	20 (9)

(*continued*)

Table 1. (Continued)

Characteristics	Total sample N = 7,120 (%)	Rural–urban category		
		Urban N = 6,643 (%)	Large rural N = 265 (%)	Small rural N = 212 (%)
Physical activity (MET/week)				
None	1,030 (14)	940 (14)	52 (20)	38 (18)
> 0–3.75	987 (14)	922 (14)	41 (15)	24 (11)
3.75–8.75	1,411 (20)	1,316 (20)	53 (20)	42 (20)
8.75–17.5	1,586 (22)	1,484 (22)	62 (23)	40 (19)
≥17.5	1,744 (24)	1,648 (25)	41 (15)	55 (26)
Hysterectomy				
No	4,398 (62)	4,120 (62)	159 (60)	119 (56)
Yes	2,717 (38)	2,518 (38)	106 (40)	93 (44)
Bilateral oophorectomy				
No	5,700 (80)	5,320 (80)	212 (80)	168 (79)
Yes	1,277 (18)	1190 (18)	47 (18)	40 (19)
Hormone therapy use				
Never	2,802 (39)	2,611 (39)	97 (37)	94 (44)
Past user	1,077 (15)	997 (15)	42 (16)	38 (18)
Current user <5 years	841 (12)	788 (12)	31 (12)	22 (10)
Current user 5 to <10 years	826 (12)	783 (12)	28 (11)	15 (7)
Current user ≥10 years	1,569 (22)	1,459 (22)	67 (25)	43 (20)
Oral contraceptive use				
No	4,235 (59)	3,972 (60)	146 (55)	117 (55)
Yes	2,885 (41)	2,671 (40)	119 (45)	95 (45)
Aspirin use				
No	5,607 (79)	5,244 (79)	201 (76)	162 (76)
Yes	1,513 (21)	1,399 (21)	64 (24)	50 (24)
NSAID use				
No	4,744 (67)	4,453 (67)	159 (60)	132 (62)
Yes	2,376 (33)	2,190 (33)	106 (40)	80 (38)
Current diabetes				
No	6,828 (96)	6,378 (96)	252 (95)	198 (93)
Yes	287 (4)	261 (4)	13 (5)	13 (6)
Cholesterol medication use				
No	5,748 (81)	5,369 (81)	208 (78)	171 (81)
Yes	939 (13)	874 (13)	38 (14)	27 (13)
Myocardial infarction				
No	6,970 (98)	6,504 (98)	259 (98)	207 (98)
Yes	147 (2)	136 (2)	6 (2)	5 (2)
Angina				
No	6,684 (94)	6,237 (94)	246 (93)	201 (95)
Yes	376 (5)	347 (5)	19 (7)	10 (5)
Charlson comorbidity index (modified)				
0	4,178 (59)	3,921 (59)	150 (57)	107 (50)
1+	2,775 (39)	2,564 (39)	110 (42)	101 (48)

DM, dietary modification; E+P, estrogen + progesterone; HS, high school; GED, general equivalency diploma; IQR, interquartile range; MET, metabolic equivalent values; NSAID, nonsteroidal anti-inflammatory drugs; OS, observational study.

participation (HT, dietary modification, and calcium/vitamin D) were included in multivariable models.

Effect modifiers

Social strain was derived from a validated measure of negative aspects of social relationships[20] and was measured with four questions at baseline: How many of the people who are important to you (1) get on your nerves, (2) ask too much of you, (3) did not include you, and (4) try to get you to do things you do not want to do. Answers were coded on a Likert scale and responses ranged from 1 (none) to 5 (all). A summary score was estimated by summing individual items, with higher scores representing more social strain (range of scores: 4–20, Cronbach's alpha: 0.71).

Social support was assessed with a nine-item questionnaire from the medical outcomes study.[39] Participants reported how often specific types of social support were available to them, including emotional, affection, tangible support, and positive interactions. Responses ranged from 1 to 5 for each item, and a composite score was calculated by summing the nine items, with higher scores representing more social support (range of scores: 9–45, Cronbach's alpha: 0.93).

Analysis

Given that the WHI data have not been described by RUCA, we summarized distributions of several participant sociodemographic and clinical characteristics (not limited to covariates of interest) by RUCA category, for future

hypothesis generation. Stage at breast cancer diagnosis was dichotomized as early (*in situ* and local) versus late (regional and distant). For descriptive purposes, we included dichotomized social strain and social support at the median (low versus high), given that no established cut-points exist,[40] and for consistency with previously published research.[26] However, we used the continuous versions of social support and strain variables in our logistic regression models. The assumption of linearity in the logit was assessed graphically (using univariable Lowess plots, plots of the estimated logistic regression coefficients vs. approximate quartile midpoints) as well as using the method of fractional polynomials,[41] no serious deviations were noted. Unadjusted and adjusted (for all covariates mentioned earlier) logistic regression models estimated odds ratios (ORs) of late versus early stage at breast cancer diagnosis and 95% confidence intervals (95% CI), comparing women across the rural–urban continuum. Separate interaction terms were included in the models to test whether the impact of rural–urban residence on stage at breast cancer diagnosis was modified by social strain or social support; we present stratified results if warranted. Analyses were performed using SAS/STAT software, Version 9.4 of the SAS System for Windows (SAS Institute, Inc., Cary, NC).

Results

Tables 1 and 2 show the distribution of sociodemographic and psychosocial factors, health behaviors and health history, and clinical indicators in postmenopausal women with incident breast cancer from the WHI, stratified by rural–urban residence (urban, large town, and small town). A higher proportion of younger women (aged 50–59 years) and a lower proportion of the oldest women (aged 70–79 years) resided in small rural towns than urban and large rural towns. In comparison to the urban population, greater proportions of the small and large rural study participants were white. In addition, relative to their urban and large rural counterparts, a larger proportion of women residing in small rural areas had not earned at least a high school diploma or GED, and reported having high social strain and high social support.

Regarding health history and health behaviors, the proportion of women with a family history of breast cancer was lower among urban women than among their small and large rural counterparts. Elevated breast cancer risk as indicated by Gail risk scores >1.67 occurred more frequently among women residing in large rural areas versus others. Greater proportions of small rural town women reported never smoking, being a nondrinker, never using HT, having received a hysterectomy, having medical comorbidities (as indicated by the Charleston comorbidity index), and participating in the estrogen-alone trial. A smaller proportion of large rural town residents reported engaging in high physical activity (≥17 metabolic equivalent values [METS]/week) than residents of urban and small rural towns. A smaller proportion of the women who resided in small towns participated in the diet modification trial, and reported ''excellent/very good'' self-

Table 2. Clinical Characteristics of Women with Incident Breast Cancer by Rural–Urban Residence at Time of Diagnosis; Women's Health Initiative (N=7,120), 1993–2014

Characteristics	*Total* N=*7,120 (%)*	*Rural–urban category*		
		Urban N=*6,643 (%)*	*Large rural* N=*265 (%)*	*Small rural* N=*212 (%)*
Approximate age (years) at diagnosis				
50 to <60	995 (14)	940 (14)	27 (10)	28 (13)
60 to <70	3,089 (43)	2,858 (43)	134 (51)	97 (46)
70 to <80	2,648 (37)	2,480 (37)	90 (34)	78 (37)
≥80	388 (5)	365 (5)	14 (5)	9 (4)
SEER stage				
In situ	1,210 (17)	1,122 (17)	45 (17)	43 (20)
Local	4,178 (59)	3,901 (59)	156 (59)	121 (57)
Regional	1,331 (19)	1,240 (19)	55 (21)	36 (17)
Distant	63 (1)	57 (1)	1 (0)	5 (2)
Morphology—grade				
1: Well differentiated	1,421 (20)	1,337 (20)	43 (16)	41 (19)
2: Moderately differentiated	2,481 (35)	2,304 (35)	95 (36)	82 (39)
3: Poorly differentiated	1,583 (22)	1,477 (22)	64 (24)	42 (20)
4: Anaplastic	476 (7)	441 (7)	22 (8)	13 (6)
Unknown/not done/missing	1,159 (16)	1,084 (16)	41 (15)	34 (16)
Hormone receptor status				
ER/PR+	3,605 (51)	3,369 (51)	138 (52)	98 (46)
ER+/PR−	802 (11)	756 (11)	20 (8)	26 (12)
ER−/PR+	83 (1)	77 (1)	3 (1)	3 (1)
ER/PR−	792 (11)	721 (11)	37 (14)	34 (16)
Borderline/unknown/missing ER and/or PR status	1,838 (26)	1,720 (26)	67 (25)	51 (24)
HER-2/Neu				
Positive	693 (10)	638 (10)	37 (14)	18 (8)
Negative	2,919 (41)	2,735 (41)	97 (37)	87 (41)
Borderline/unknown/missing	3,508 (49)	3,270 (49)	131 (49)	107 (50)

ER, estrogen receptor; PR, progesterone receptor; SEER, surveillance, epidemiology, and end results.

Table 3. Relationship Between Rural–Urban Residence and Stage at Breast Cancer Diagnosis, and Interactions with Social Strain and Social Support; Women's Health Initiative ($N = 6782$), 1993–2014

Rural–urban comparisons	*Unadjusted OR (95% CI)*	*Adjusted OR (95% CI)*
Urban	1.03 (0.73–1.46)	1.08 (0.76–1.53)
Large town	1.11 (0.71–1.75)	1.16 (0.74–1.84)
Small town	1.00 (reference)	1.00 (reference)
Urban	0.93 (0.69–1.25)	0.93 (0.68–1.26)
Large town	1.00 (reference)	1.00 (reference)

Social strain X RUCA p for interaction: 0.17; social support X RUCA p for interaction: >0.99.

Adjustments: age at screening, education, insurance, and trial membership.

CI, confidence interval; OR, odds ratio; RUCA, rural–urban commuting area.

rated health. Higher proportions of urban women than women in either rural category reported oral contraceptive use and receiving a mammogram in the past 2 years.

There also were rural–urban differences in sociodemographic and clinical characteristics of women with incident breast cancer (Table 2). The distribution of approximate age at incident breast cancer diagnosis was similar across rural–urban areas, except that women who lived in large rural towns were more often between 60 and 69 years old. In addition, a greater proportion of women residing in large rural towns had HER-2/Neu positive cancers and regional stage breast cancer. In contrast, a smaller proportion of women residing in large rural towns had HER-2/Neu negative cancers, and had well-differentiated tumors, compared with those of urban and small rural residents. Among women residing in small rural towns, a greater proportion of tumors were moderately differentiated, a smaller proportion had estrogen receptor/progesterone receptor positive (ER/PR+) tumors and a larger proportion had estrogen receptor/progesterone receptor negative (ER/PR–) tumors relative to their urban and large rural counterparts.

Of the sociodemographic, behavioral, and clinical covariates examined, only age at screening for enrollment into WHI was significantly associated with stage at diagnosis, with older age at screening being protective (OR for age 60–69 years vs. <50–59 years = 0.79; 95% CI: 0.69–0.91; OR for age >70–79 years vs. <50–59 years = 0.82; 95% CI: 0.69–0.96; overall $p = 0.003$). There was no significant association between rural–urban residence and stage at breast cancer diagnosis (Table 3). Furthermore, there was no evidence that the association between rural–urban residence and stage at breast cancer diagnosis was modified by either social strain or social support.

Discussion

We describe, for the first time, the distribution of sociodemographic and clinical characteristics of participants of WHI participants, by the most popular and advantageous method used to define rural–urban residence (RUCA taxonomy), in cancer research.[14,15] We found little evidence of an association between rural–urban residence and stage at breast cancer diagnosis, among postmenopausal women, regardless of social strain or social support.

Our null main effects are consistent with three studies that have examined the effect of rural–urban residence (using the RUCA classification system) on stage at breast cancer diagnosis. The earliest study by Celaya et al. used data from the predominantly rural state of New Hampshire ($n = 5{,}966$), and the authors noted limitations stemming from their use of cancer registry data from 1998 to 2005 and lack of information on mammography use for women with incident cancers.[42] Similarly, Henry et al. used a 10-state cancer registry data set covering the period 2004–2006 ($n = 161{,}619$) and, similar to the study by Celaya, did not have mammography utilization data.[1] Finally, Markossian and Hines used 1992–2007 data from urban (Atlanta) and rural Georgia National Cancer Institute's SEER program registries ($n = 23{,}500$); however, their results are not generalizable and are based on aggregate county-level data on rural–urban residence.[43]

Although the existing literature on the impact of rural–urban residence on stage at breast cancer diagnosis has not examined potential moderation by social support and social strain, these social factors have been shown to impact general as well as cancer-specific health behaviors[21–27] and health outcomes.[28–30] Given this literature, it is theoretically plausible that these factors might exacerbate (social strain) or buffer against (social support) the effects of rural residence on stage at breast cancer diagnosis. We add to the extant literature on this topic a by testing novel effect modification hypotheses, and using data from a large geographically diverse multiracial/ethnic cohort of postmenopausal women in which mammography utilization data are available. Future studies with more variability in rural–urban residence may be able to confirm our null interaction effects or extend our findings by providing support for the joint effects.

The following limitations of this study should be considered. First, we could not use the **T**umor growth, lymph **N**odes, and distant **M**etastasis (TNM) breast cancer staging system[44] due to missing data on affected lymph nodes at the time of diagnosis. Given the multidecade follow-up of the WHI, and RUCA codes that are not fully comparable over time, we also had to limit exposure classification to data from Census year 2000 to optimize our sample size. We were, therefore, unable to exploit the longitudinal nature of the WHI or answer research questions about risk of breast cancer associated with urban versus rural residence. Certainly, rural geographies are not monolithic,[45] and although the WHI study participants resided in a large number of states in the United States, the entire country was not represented in the sample, which may limit the generalizability of our findings. Given sample size constraints, we were also unable to assess potential effect modification by geographic region or race/ethnicity. Finally, 93% of the study population resided in urban areas, which may have limited our power to detect rural–urban differences in stage at breast cancer diagnosis.

This study also has several strengths. First, we have comprehensive sociodemographic and cancer risk factor assessment, and central adjudication of incident cancers. We also applied a popular rural–urban classification taxonomy to a large multiethnic well-characterized cohort of postmenopausal women from across 40 clinical centers in the United States, which will be useful for future research. Finally, we tested novel effect modification hypotheses, and sought to identify predictive and protective factors for the association between rural–urban residence and stage at breast cancer diagnosis.

In conclusion, the ''rural penalty,'' in terms of stage at breast cancer diagnosis, was not apparent among WHI participants, and there was little evidence of effect modification by social support or social strain. Future studies should consider effect modification by other modifiable factors to identify putative heterogeneity in the association between rural–urban residence and stage at breast cancer diagnosis. This information could be useful in informing future intervention studies focused on the cancer control continuum.

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