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Review

Rural Residence and Cancer Outcomes in the United States: Issues and Challenges

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Abstract

"Neighborhoods and health" research has shown that area social factors are associated with the health outcomes that patients with cancer experience across the cancer control continuum. To date, most of this research has been focused on the attributes of urban areas that are associated with residents' poor cancer outcomes with less focused on attributes of rural areas that may be associated with the same. Perhaps because there is not yet a consensus in the United States regarding how to define "rural," there is not yet an accepted analytic convention for studying issues of how patients' cancer outcomes may vary according to "rural" as a contextual attribute. The research that exists reports disparate findings and generally treats rural residence as a patient attribute rather than a contextual factor, making it difficult to understand what factors (e.g., unmeasured individual poverty, area social deprivation, area health care scarcity) may be mediating the poor outcomes associated with rural (or non-rural) residence. Here, we review literature regarding the potential importance of rural residence on cancer patients' outcomes in the United States with an eye towards identifying research conventions (i.e., spatial and analytic) that may be useful for future research in this important area. *Cancer Epidemiol Biomarkers Prev; 22(10); 1657–67. ©2013 AACR.*

Introduction

In their 2003 landmark report entitled "Unequal Treatment; Confronting Racial and Ethnic Disparities in Healthcare", the Institute of Medicine acknowledged that disparities in health status and health care use exist for many subpopulations in the United States (1). The report identified characteristics of patients whose disparities were the most striking and this included patients who were black, of advanced age, and of low socioeconomic status (SES). In addition, the report identified "rural residence" as a potential risk factor for patient health-based disparities. Specifically, the report stated that "for all patients, process of care (as assessed by measures of physician and nurse clinical decision-making, technical diagnostic and therapeutic processes, and monitoring processes) were of lower quality in rural hospitals and best in urban teaching hospitals (1)." While the report brought attention to the fact that disparities exist between residents of urban and rural areas, most emblematic examples focused on outcomes from cardiac care and specifically few described patient outcomes from cancer and cancer care according to rural residence.

Cancer is the second leading cause of death in the United States and thus the disparities that exist between groups of patients deserve close study (2). Increasingly, researchers in oncology have identified significant disparities that exist in the diagnosis, treatment, and survival among different groups of patients. There are large literatures on race-based disparities, economic-based disparities, and age-based disparities in cancer care. However, the existing literature describing rural–non-rural disparities is comparatively nascent and methodologically inconsistent. Perhaps, not surprisingly, findings have been inconsistent across cancer sites and across the cancer continuum. Here, we summarize the existing literature regarding the outcomes of patients with cancer residing in rural locations and in so doing seek to (i) bring clarity to the definition of "rural" and (ii) explore the extent to which patient compositional factors versus the contextual factor of "rural" may mediate any differences in cancer outcomes.

Definitions—What is "Rural"?

Conventions used to define "rural" in cancer outcomes research have primarily relied on either (i) methods developed by government agencies that use administrative geospatial units or (ii) intuitive methods developed by individual research teams related to travel distance from patient residence to treatment center (3–5).

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Geospatial units

The US Census Bureau defines rural areas as those that are not "urban" and at its most refined level of granularity is the Census block. Specifically, rural is defined as all territory, population, and housing units located outside of urban areas (UA) or urban clusters (UC; ref. 6). The UAs and UCs are determined by population density in census areas (i.e., population of ≥50,000 individual/square mile and population ≥10,000 individual/square mile, respectively). Core census block groups or census blocks that have a population density of at least 1,000 individuals/square mile and surrounding census blocks that have an overall density of at least 500 individuals/square mile are considered urban. While this seems straight forward, given that census blocks and core census block groups are smaller components of the larger spatial measure of census tract, there are situations where a single census tract may be composed of both urban and non-urban (i.e., rural) core census block groups or census blocks. Therefore, any taxonomy that relies solely on the census tract to define "rural" is imperfect even by US Census standards. This is highly relevant to research that uses the US Census' so called Summary File 3 (SF3) data. These data are comprehensive in their coverage of the United States, but are reported at the level of census tract most consistently.

Other administrative conventions rely on the Office of Management and Budget's (OMB) metropolitan/non-metropolitan taxonomy which defines a metropolitan area as one that must contain one or more central counties with UAs (i.e., population of ≥50,000 individual/square mile). Non-metropolitan areas are outside the boundaries of metropolitan areas (core UAs) and are subdivided into 2 types, "micropolitan areas" (UCs) and "noncore counties". The reliance on component county features and geographies in distinguishing metropolitan (i.e., urban) and non-metropolitan (i.e., non-urban) is appealing because (i) county boundaries remain fairly stable over time and (ii) national health datasets (e.g., Bureau of Labor Statistics, County Health Rankings) use counties as their geographic units, something that may facilitate research in this area (7). The concern with using counties is that population density within a county can vary such that larger "counties" may include aspects of both urban and rural area. Relatively, a "metropolitan area" may include non-metropolitan counties (5, 8). These facts suggest these methods of defining rural and urban have at least some degree of imprecision and thus may not be useful conventions for subsequent research.

The US Department of Agriculture's (USDA) Rural-Urban Commuting Area Codes (RUCA) definition of rural relies on a combination of area attributes including (i) population density (individuals/square mile), (ii) proximity to an UA (as defined by the US Census Bureau), and (ii) daily commuting patterns (9). RUCAs are measured at the census tract (CT), which may be transformed into Zip Code Tabulation Areas which are themselves geographically smaller than counties and easier to use with datasets that contain limited information on the health care provider location and/or patient residence (i.e., postal code rather than full street address; ref. 7). This method of grading rurality or urbanicity is an appealing research convention because it determines the geospatial unit through functional relationships (i.e., proximity to UAs and commuting rates) as well as population density and it is at a smaller geographic unit than the OMB (5, 8). The USDA has a second and related taxonomy, the Rural Urban Continuum Codes (RUCC; also known as Beale's codes), which are defined by (i) population size (ii) proximity to an UA, and (iii) adjacency to a metropolitan area. RUCCs take into account the standard OMB categories and subdivide them into 3 metropolitan and 6 non-metropolitan categories which can help to minimize the effects of variations in county size (10). RUCCs are very similar to OMBs, with the difference being that RUCCs define geographic units at a finer granularity. So it is not surprising to learn that the findings of studies using the OMB definition of rural may differ from the findings of studies using the RUCC definition. Specifically, two studies looking at stage at diagnosis of colorectal cancer in rural versus non-rural patients came to opposite conclusions (11, 12). A study using the Nebraska Cancer Registry and the OMB convention found that metropolitan patients were significantly more likely than non-metropolitan patients to be diagnosed at an early stage of colorectal cancer (12). However, a study using the Surveillance, Epidemiology, and End Results (SEER) data and RUCC convention found that metropolitan patients compared with non-metropolitan patients were more likely to present at a later stage of colorectal cancer (11). While it is tempting to conclude that this difference in results relate to geospatial magnitude OMB versus RUCCs, it is also true that different regions of the country were studied and if the effect of rural residence varies by state then region of the country could confound the findings. However, given the substantial overlap in definitions, studies using RUCAs and RUCCs tend to report consistent findings (4, 5, 13–16).

In Australia, there is an established convention determining "rural" in studies of health care called the Accessibility/Remoteness Index of Australia (ARIA). The ARIA defines area "remoteness" based on access along the road network to urban centers [centers with a population of ≥5,000 individuals/square kilometer (km), termed "service centers" in the literature] and can use a variety of spatial units (e.g., Australian census collection districts, statistical local areas/local government areas, postal codes, and/or full street addresses). This method is appealing because it (i) looks at "remoteness" as a characteristic of a geographic location relative to areas where health care is likely to be available (e.g., urban centers) as opposed to basing it on population size or density and (ii) is flexible with respect to the level of granularity desired. That is, it can characterize an area as broad as a census collection district to one as refined as an individual patient address. Other countries also use classifications based on government census data and units (17–20).

Because in the United States there is not a single established convention for defining rural in studies of cancer outcomes, the existing literature contains a mixture of studies that define rural in any one of a number of ways making comparisons of results across studies challenging and their generalizability unclear. Numerous papers acknowledge the heterogeneity in definitions of "rural" and a prior review has summarized this literature with respect to cancer outcomes (21). To our knowledge, unlike Australia, U.S. researchers in the field of rural health have yet to propose a specific method to define "rural" in population-based cancer research. The most common measures of rural health that are used by researchers studying cancer risk, patterns of care, and outcomes are; (i) RUCAs; (ii) OMB's definition; (iii) RUCCs; and (iv) census tracts. Table 1 summarizes these measures. Others have sought to determine associations between cancer patients' outcomes and other area attributes that may capture rurality or remoteness in other ways including land usage (e.g., farming), the ratio of health services to patients, and road distance to the nearest urban center (similar to the Australian ARIA) as a means of consistent measurement (22, 23).

Travel distance

Patient travel distance from their exact home address, their census tract centroid, or the centroid of other larger geospatial units to available health care has also been used to study associations between rural residence (or "remoteness") and a variety of cancer outcomes. Using patient travel distance as a measurement unit rather than census blocks, census tracts, or counties may control for populations that may include both non-rural and rural communities. Interestingly, ARIA, which has been the consistent rural–urban measurement system in Australia, takes into account travel distance by including daily commuting patterns. It may be that a measurement unit that simultaneously accounts for county size, population density, and travel distance is most beneficial in defining patient residence.

In summary, while investigators have acknowledged the difficulties in accurately defining rural for population-based cancer research (24), they have yet to agree upon which of these methods is most effective in doing so. It is critical to the results of rural-urban (or rural-non-rural) disparities research that rural be defined consistently so that researchers can begin to understand what the association is (if any) between rural residency and cancer. Because the RUCA incorporates *both* population density and an element of average population travel distance, we see it as an appealing geospatial convention for population-based cancer research. For patient-level research where it is possible to calculate exact travel distances, using travel distance as a proxy for rural may be more appealing as it can be tailored to the individual and is a more refined measure of individuals' access to care which may be a mediator for the effects of rural residence on patients' cancer outcomes.

Analytic Approaches

Broadly, the existing analytic conventions used in rural–non-rural cancer research are either (i) single-level regression analyses in which researchers treat rural residence as an attribute of the patient (i.e., a compositional factor rather than a contextual factor) and may or may not adjust the SEs of their estimates to acknowledge the non-independence due to membership within a group (e.g., patients clustered within census tracts) or (ii) hierarchical or multi-level regression analyses that permit simultaneous evaluation of the contribution of individual patient compositional factors at level I (e.g., age, sex, race, comorbidity) and area contextual factors at level II (e.g., residence in a rural region) while adjusting SEs appropriately for the non-independence of observations. Although, to date, the majority of rural–non-rural disparities research is composed of single-level analyses, there is growing research that relies on the more analytically rigorous multi-level analytic approach (25, 26).

Single-Level Regression—"Rural" as a Patient Attribute

Residence in a "Rural" geospatial unit

Here, we summarize literature in rural–non-rural cancer disparities research according to selected phases of the cancer control continuum (i.e., screening, follow-up of abnormal screening tests, incidence, stage at diagnosis, treatment, and survival).

Screening

There is considerable evidence that residents of rural areas have lower levels of utilization of cancer screening methods. Mammography breast cancer screening is less common among residents of rural areas, compared with those of urban areas (27–29). Results from Nuño and colleagues suggest that, compared with urban Hispanic women, rural Hispanic women were less likely to have had a mammogram within one year and a Pap smear within 3 years (27). Fan and colleagues found that, among elderly Medicare beneficiaries, rurality was significantly negatively associated with colorectal cancer screening, but not mammography, even after controlling for patient and area level characteristics (28).

Follow-up of abnormal screening tests

Follow-up after an abnormal screening test is needed to ensure that detected abnormalities do not progress to cancer or early stage cancers get treated early while cure with limited morbidity is still possible. In a study conducted within the Ohio State University (OSU) Center for Population Health and Health Disparities, women with abnormal Pap tests from 18 Appalachia Ohio clinics were followed to determine if they received testing, by abstracting information from medical records for up to 3 years after their initial abnormal Pap test and comparing treatment type and time since diagnosis to what was recommended by the American Society for Colposcopy and

Table 1. Rural definitions

Definition	Definition description	Geographic unit used	Pros and cons for cancer research
U.S. Census Bureau: Urban and Rural Areas	The Census Bureau's classification of rural consists of all territory, population, and housing units located outside of urbanized areas and urban clusters. Urbanized areas include populations of at least 50,000, and urban clusters include populations between 2,500 and 50,000. The core areas of both urbanized areas and urban clusters are defined based on population density of 1,000 per square mile and then certain blocks adjacent to them are added that have at least 500 persons per square mile.	Census Block and Block Groups	Pros: Census geography is more stable than ZIP code areas due to the fact that it changes over 10-year intervals rather than annually. Census geography is also the smallest geographic unit available. Cons: It is difficult to implement census definitions of rural because census geographical information is not often used by programs such as Medicare, Medicaid, and insurance companies.
Economic Research Service, U.S. Department of Agriculture & WWAMI Rural Health Research Center: RUCAs	This classification scheme utilizes the U.S. Census Bureau's urbanized area and cluster definitions and work commuting information. The RUCA categories are based on the size of settlements and towns as delineated by the Census Bureau and the functional relationships between places as measured by tract-level work commuting data. This taxonomy defines 33 categories of rural and urban census tracts.	Census Tract, ZIP Code approximation available	Pros: RUCAs encompass population density, urbanization, and daily commuting. This method provides a measure of functional relationships while using a more specific geographic unit than the OMB's taxonomy. If using the ZIP code approx. - ZIP code areas are more geographically specific than boundaries created by county lines. ZIP codes are also easier to use with programs that rely on the provider/beneficiary address. Cons: (see above for census tract) If using the ZIP code approximation- ZIP codes often change annually.
U.S. Office of Management and Budget (OMB): Core-based statistical areas (i.e., metropolitan and non-metropolitan areas)	A metropolitan area contains a core urban area with a population of 50,000 or more. Non-metropolitan counties are outside the boundaries of metropolitan areas and are subdivided into two types, micropolitan areas and noncore counties. Micropolitan areas are urban clusters with a population of at least 10,000, but less than 50,000.	County	Pros: National health data sets use counties as their geographic unit and county boundaries remain very stable over time.Cons: County size varies and larger counties may include both urban and rural areas.
Economic Research Service, U.S. Department of Agriculture: Rural–Urban Continuum Codes (Beale Codes)	This classification scheme classifies counties and county equivalents OMB metropolitan–non-metropolitan status and then further subdivides into three metropolitan and six nonmetropolitan groupings by the population size of the metropolitan area and adjacency to another metropolitan areas.	County	Pros: RUCCs, like RUCAs, also distinguish counties by size, degree of urbanization, and proximity to metropolitan areas. RUCCs take into account the OMB categories and subdivide them further which can help to minimize the effects of variations in county size.

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Table 1. Rural definitions (Cont'd)

Definition	Definition description	Geographic unit used	Pros and cons for cancer research
			Cons: (see above for OMB)
Office of Rural Health Policy, U.S. Department of Health and Human Services: RUCA adjustment to OMB metropolitan and non-metropolitan definition	This method uses RUCAs 4–10 to identify small towns and rural areas within large metropolitan counties. In addition, census tracts within metropolitan areas with RUCA codes 2 and 3 that are larger than 400 square miles and have population density of less than 30 people per square mile are also considered rural.	Census tract within OMB metropolitan counties	Pros: This method uses the metropolitan counties defined by the OMB in addition to RUCAs, to create a more specific definition and to define the rural/urban areas that may exist within a large metropolitan county. Cons: It is difficult to implement census definitions of rural because census geographical information is not often used by programs such as Medicare, Medicaid, and insurance companies.
ARIA: Accessibility/Remoteness Index of Australia	This method defines five categories of remoteness based on road distance to service centers (urban areas with a population of 5,000 or more), and is available for a variety of geographical units including localities, Census collection districts, statistical local areas(SLA)/local government areas(LGA) and postcodes.	A variety of Australian government units	Pros: ARIAs, similar to RUCAs, encompass population density, urbanization, and daily commuting. Cons: County size defined by the boundaries created by the SLAs and LGAs may vary and can contain both rural and urban areas.

Cervical Pathology Consensus Guidelines (30). Among 283 women with an abnormal Pap test, 70% received some type of follow-up, 60% received appropriate recommended guidelines; however, only 47% received the guideline-recommended treatment within the recommended timeframe for their specific abnormality. That is, less than half of the women received guideline-recommended care in a timely manner. These findings are in contrast with those of urban women within the Patient Navigation Research Program where fully 70% to 80% of control women with screening-detected cervical abnormalities resolved (experienced resolution of their abnormalities via guideline-recommended care) within one year (31, 32).

Incidence

There is no known published, comprehensive assessment comparing cancer incidence rates in rural areas to those in urban or metropolitan areas, such as that which could be possible using the Surveillance, Epidemiology, and End Results (SEER) Program. However, there are reports suggesting differences in cancer incidence based on rural residence. For example, Singh found that cervical cancer incidence rates among women residing in small urban areas and rural areas were 6% and 15% higher than those of women residing in metropolitan areas; furthermore, these rates were 28% and 61% more among non-Hispanic white and black women in rural areas, respectively, compared with those of their counterparts residing in metropolitan areas (33). Hausauer and colleagues reported that, between 2001 and 2004, the U.S. invasive breast cancer incidence rate decreased 13.8% among women ages 50 to 74 years in urban areas and 7.5% among women of the same ages in rural areas (34). It is difficult to interpret this difference; however, as it is likely due to a complex set of factors which vary according to urban/rural status, including reduced levels of initiation of, or discontinuation of, postmenopausal estrogen/progestin hormone therapy, and reductions in mammography screening, possibly due to screening saturation.

Stage at diagnosis

Perhaps as a by-product of the use of conflicting methods to define rural, the literature regarding the importance of individuals' rural versus non-rural residence and subsequent cancer outcomes in the United States is inconsistent. For example, there is a divide within the current individual-level research as to whether rural or non-rural patients present with a more advanced stage of disease at diagnosis. This divide may stem from issues pertaining to methods as well as variation in what tumor types are being studied. For instance, in a national study conducted from 2000–2003 looking at colorectal cancer and lung cancer using RUCCs method of measuring rurality, it was found that non-rural patients were more likely to present at a later stage compared with rural patients (11). However, a previous study evaluating stage at diagnosis for colon cancer in North Carolina 1996–2000 using zip codes and census tracts as measures of rurality concluded that distribution of stage did not vary by the rurality of patients' place of residence (35). It is tempting to conclude that the difference in results seen here relates solely to the difference in methods used (RUCCs vs. zip codes/census tracts); however, it is also likely that the difference in time periods and regions of the country studied may have impacted the variation in results.

Treatment

Results of existing literature show that the patterns of care associated with rural residence vary by rural definition, cancer type, stage at diagnosis, and geographic residence. The most consistent finding pertains to use of radiotherapy. For example, several groups have shown that compared with other women with breast cancer, women with breast cancer who reside in rural areas (defined by RUCCs and zip codes/census tract data) and/or live further away from radiation treatment facilities are more likely to receive mastectomies rather than breast-conserving surgery (BCS) which requires daily treatments with radiotherapy over 6 consecutive weeks (16, 36–38). Similarly, women living a greater distance from radiotherapy centers were less likely than those living closer to receive guideline-indicated curative-intent postsurgical radiotherapy (36, 37). Another study using RUCCs and looking at patients with endometrial cancer has found that rural patients are less likely to receive radiotherapy following surgery (15). Similarly, rural patients with prostate cancer are less likely to receive radiotherapy than non-rural patients (39). A study recently reported by Cetnar and colleagues found that among men diagnosed with localized prostate cancer, there were no differences in the receipt of curative therapy—curative resection, radiotherapy, or surgery—among rural men versus urban men (40). Wisconsin, however, is the exception to what is commonly found in rural setting—95% of all residents live within 15 miles of a hospital (41–43). Thus, access to care for both rural and urban patients was assured. Quality of care was not determined (41). Conversely, when looking at other modalities of cancer care (e.g., chemotherapy and surgery), rurality seems less important. For example, rural residence (defined by RUCA) at diagnosis was not associated with receipt of surgery or chemotherapy for patients across all stages of lung cancer (8). The finding is not surprising given that radiation is typically administered daily for 6 consecutive weeks, whereas surgery occurs generally once and chemotherapy occurs once every 3 to 4 weeks. Given the variation in findings, it is apparent that when studying rural/non-rural discrepancies and cancer treatment, it is critical to not only accurately define rural but also to differentiate between modalities of care as the existing literature suggests that use of radiotherapy may be most sensitive to rural residency.

In addition to acknowledging the difference in treatment modality, it is important to know that the effect of patient factors and cancer outcome may vary by rural/non-rural residence and thus impact treatment choices differentially. For example, rural patients of lower SES may be at an even greater disadvantage than their non-rural counterparts (i.e., there may be a differential effect of poverty based on urban/rural status).

Survival

Findings related to cancer mortality in patients with melanoma, lung, and breast cancer from studies using individual-level methods and Census tract definitions of rural have been relatively consistent in concluding that after adjusting for individual factors like demographics, comorbidity, treatment, and stage, rural residence does not directly influence cancer-related mortality, rather patient-level factors (i.e., poverty, age, race) play more of a role (8, 44, 45). This finding contradicts the results of a study looking at disease-free survival given that the percentage of patients across all stages of endometrial cancer who were never disease-free was higher among rural (defined by RUCCs) residents (15).

The special case of residence in the Appalachian region of the United States

Approximately 42% of the Appalachian region of the United States is rural. There are considerable cancer-related disparities in Appalachia, a region containing 24 million residents in 420 counties of 13 states. Consistent findings support higher cancer incidence and mortality rates for many sites/types of cancers in the Appalachian region, as compared with the rest of the United States (46, 47). These disparities are most apparent in the Central Appalachian region (46) and are strongest for cancers of the cervix, colon and rectum, and lung and bronchus, with incidence and mortality rates for these cancers greater in the majority of the states' Appalachian areas compared with corresponding non-Appalachian areas (47). Socioeconomic differences and rurality may at least partially explain these disparities although exact mediators of the findings have been described (e.g., decreased availability of screening facilities, inability to afford travel to screening centers).

Patient Travel Distance

Stage of disease at diagnosis

Patient travel distance has also been used as a way to assess differences between rural and non-rural patients with respect to cancer stage at diagnosis. Again, results vary depending on the type of tumor. Studies looking at breast (44, 48) and multiple cancers (5) argue that travel distance (i.e., from patient home to the nearest provider) is not associated with stage of disease at diagnosis, whereas a study looking at melanoma shows that increasing distance from a provider results in a more advanced stage of disease at diagnosis (45).

Treatment

It is clear that patients living in rural areas must travel longer distances to health care facilities providing cancer care (3, 4). As noted above, there is now substantial research showing that patient travel distance from home to closest radiotherapy center is a salient factor in the local control women with locoregional breast cancer receive. That is, patients with breast cancer living a longer distance from radiotherapy facilities are more likely to undergo a mastectomy rather than BCS and those living a longer distance from radiotherapy facilities who require curative-intent postoperative radiation (i.e, following either BCS or mastectomy) therapy are less likely to receive it (36–38, 49).

Survival

Research that studies cancer patients' survival as a function of travel distance shows that there is no difference between rural and non-rural patients survival yet there is a difference in survival depending on the size of the hospital in which they were treated, with smaller hospitals being associated with poorer survival (15). This same study found that rural residents were more likely to be treated at a smaller hospital (15). This research raises the hypothesis that prior work showing that the poor outcomes for cancer patients living in rural regions may have been mediated by small hospital size.

Multi-Level Regression—"Rural" as a Contextual Attribute

Where a person lives in the United States is associated with their health and the health care they receive net of their individual attributes that put them at risk for disease and/or receipt of inadequate care. Supraindividual geographic variation in health and health care has been established by nearly 40 years of research from varied scientific disciplines (50–56). What mediates observed supraindividual geographic variation in health and health care is less clear. Social epidemiologists have published compelling research that credits supraindividual neighborhood factors like "poverty" as contributing to the health and health care use of individuals living in these social geographies (53, 54). The statistical method hierarchical or multi-level regression analysis is an ideal statistical approach to such studies in which individuals are nested within a smaller number of geographic areas. The method permits simultaneous evaluation of the contribution of patient factors (e.g., age, sex, race, comorbidity) and area contextual factors (e.g., patient residence in a rural region) while adjusting SEs appropriately for the non-independence of observations associated with nested data. Possibly as a result of the conflicting methods used to define "rural" and the relative novelty of hierarchical methods, the literature using multi-level analyses to measure the importance of individuals' rural versus non-rural residence and their subsequent cancer outcomes in the United States is both inconsistent and scant. The multilevel studies often differ from one another in the demographic traits that they include in their hierarchical models (e.g., race, poverty, age). This inconsistency is critically important as patient demographics vary by rural–urban location in the United States. That is, urban areas are more likely to be black and of a lower SES (both factors are known to be associated with unfavorable cancer outcomes) than their rural counterparts (25). This means that if these patient attributes were omitted from a model, any unfavorable association between rural residence and patient cancer outcome could be confounded by unmeasured patient race and SES. Such problems of confounding are not limited to multi-level models.

Screening

Few studies have estimated the effects of area-level rural status within a multilevel model. A study of Ohio females sought to determine the effects of various contextual factors on mammography utilization (57). Modeled as a continuous variable, patients' RUCC of residence (crude or adjusted) was not found to be statistically significantly related to mammography utilization.

Incidence

The contextual effect of rurality on cancer incidence has been estimated for several cancer sites in a single study (58). "Rural", "suburban", and "metropolitan" categorizations were created from RUCCs. Compared with their counterparts living in metropolitan areas, men living in rural areas were found to have lower rates of anal cancer and women living in rural areas were found to have lower rates of oral cavity and pharynx cancer after adjusting for patient race, patient ethnicity, and county-level factors related to SES. Nonsignificant associations were found comparing rural with metropolitan residence and rates of penile, vaginal, vulvar, and female anal cancers. This research also suggests that for certain cancers there may be an interaction between race and rurality. That is, Asian and Pacific Islanders (API) residing in rural areas had higher rates of cervical and oral cavity and pharynx cancers compared with those APIs residing in metropolitan areas. Conversely, among whites, those residing in rural areas had lower rates of cervical and oral cavity and pharynx cancers compared with whites living in metropolitan areas (58). Results from a study of melanoma, however, suggest that rates of this cancer are equivalent in urban and rural counties and that there is no race rurality interaction (59).

Stage at diagnosis

There is limited literature using multi-level analysis to investigate stage of disease at diagnosis of non-rural versus rural residents. Studying twenty years worth of data from Dane County in Wisconsin, researchers found that among women living with breast cancer diagnosed between 1986 and 1990, those living in non-rural ZIP codes had more than twice the rate of *in situ* carcinoma of the breast compared to women in rural ZIP codes (12% vs. 5%). The findings were associated with increased rates of screening mammography in non-rural areas and thus consistent with a stage shift favoring lower stages of disease among non-rural women compared with rural women (26). Further, looking at the stage distribution between 1996–2000 when rates of mammography screening were more uniform across Dane County, they found that county-wide rates of BCIS were 13%–14% and did not differ by ZIP codes. In contrast, in a multi-level study estimating the odds of late-stage diagnosis with breast, colorectal cancer, lung, and prostate cancer by RUCA levels aggregated to the zip-code level, investigators found that compared with those living in the city of Chicago, residents of rural areas in Illinois had lower rates of late-stage (i.e., incurable) colorectal and lung cancers (60).

Treatment

Multi-level analyses have been used to measure the impact that individuals' race and neighborhood characteristics have on the likelihood of receiving chemotherapy for CRC (25). Through the use of hierarchical analysis, the researchers came to the conclusion that urban and suburban patients are significantly more likely to receive chemotherapy than their rural counterparts. After adjusting for individual-level variables (including race), residing in a rural location continued to be a significant negative predictor of the likelihood of receiving chemotherapy but poverty (area poverty or individual poverty) did not.

Survival

Only one known U.S. study has investigated the multilevel association between a measure of rurality and cancer survival (61). A study of Texas females failed to find a statistically significant association between cervical cancer survival and percent rural at the zip-code level (61). Similar findings for breast cancer were reported in a recent and methodologically distinct study which used sandwich estimators to correctly estimate area-level SEs. That is, researchers found that county-level "rural" was not significantly related breast cancer survival (62).

Spatial Analysis Involving "Rural"

Similar to the statistical effects that multilevel models have on SE calculations of data exhibiting possible membership processes, spatial analysis techniques have the ability to correctly estimate SEs and account for residual spatial dependence (63, 64). Spatial dependence may be present in data for various reasons, including: incorrect choice of level in multilevel analyses, unmeasured confounding, or natural spatial clustering of a given phenomenon (63, 64). In practice, the area-level spatial dependence of an individual- + area-level multilevel model is investigated and controlled if dependence is found. However, techniques may also be applied to correct for spatial dependence within individual-level point data (65) or single-level data of an area-level (64).

Only two known U.S. studies have investigated the effects of a measure of rurality on any cancer-related outcome while accounting for possible spatial dependence. One multilevel study found that county-level metropolitan ($\geq$1,000,000 population) versus non-metropolitan and urban ($\geq$50,000 population) versus non-urban were not significantly associated with childhood cancer incidence in Texas, adjusted for individual-level race and cancer diagnosis year and area-level spatial dependence (66). Similarly, null findings resulted from a single-level, ecologic analysis estimating incidence of myelodysplastic syndromes using census tract-level RUCAs (67).

Conclusions

In summary, review of the literature yields little in the way of consistent findings regarding the importance of rural residence on cancer outcomes. The one finding that seems consistent is that use of curative-intent radiotherapy is negatively associated with rural residence for women with breast and endometrial cancers as well as men with prostate cancer. The lack of consistent findings may stem from inconsistencies in (i) how rural is defined and measured and (ii) the analytic methods used. To address the disparities between rural and non-rural patients, it is critical to adopt a common metric of defining rural and likely adopt a common analytic approach. From our review of the literature, we find a scientifically sound metric of rural to be the RUCA because it incorporates both population density and travel distance and a scientifically analytic method to be multi-level regression because it lends itself to inquiry to identify mediators of any rural/non-rural disparity and adjusts SEs appropriately for nonindependence of observations that is inherent in analyses of patients living in common geospatial units. Adoption of clear conventions in defining rural and analyzing data may facilitate research so that policy makers better understand in what clinical situations rural residence puts patients at risk for suboptimal cancer outcomes and thus advance research targeted at the common goal of decreasing disparities in cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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