Multilevel analysis in rural cancer control: A conceptual framework and methodological implications

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Abstract

Rural populations experience a myriad of cancer disparities ranging from lower screening rates to higher cancer mortality rates. These disparities are due in part to individual-level characteristics like age and insurance status, but the physical and social context of rural residence also plays a role. Our objective was two-fold: 1) to develop a multilevel conceptual framework describing how rural residence and relevant micro, macro, and supra-macro factors can be considered in evaluating disparities across the cancer control continuum and 2) to outline the unique considerations of multilevel statistical modeling in rural cancer research. We drew upon several formative frameworks that address the cancer control continuum, population-level disparities, access to health care services, and social inequities. Micro-level factors comprised individual-level characteristics that either predispose or enable individuals to utilize health care services or that may affect their cancer risk. Macro-level factors included social context (e.g. domains of social inequity) and physical context (e.g. access to care). Rural-urban status was considered a macro-level construct spanning both social and physical context, as "rural" is often characterized by sociodemographic characteristics and distance to health care services. Supra-macro-level factors included policies and systems (e.g. public health policies) that may affect cancer disparities. Our conceptual framework can guide researchers in conceptualizing multilevel statistical models to evaluate the independent contributions of rural-urban status on cancer while accounting for important micro, macro, and supra-macro factors. Statistically, potential collinearity of multilevel model predictive variables, model structure, and spatial dependence should also be considered.

Keywords

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1. Introduction

Rural populations in the United States comprise as many as 59 million people (19% of the population) (U.S. Census Bureau, 2012). Compared to urban populations, people in rural areas often face a myriad of challenges that negatively affect their health, including greater levels of poverty, higher rates of uninsured status, greater distance to health care services, and poorer built environments (Charlton et al., 2015; Foutz et al., 2017; U.S. Department of Agriculture, 2019; Watson et al., 2016). Due in part to these challenges, rural populations experience cancer disparities across the cancer control continuum from prevention to incidence to survivorship and mortality (United States Department of Agriculture, 2019). Rural disparities include the following: poorer cancer-related health behaviors (e.g. smoking, sedentary behavior) (Doogan et al., 2017; Matthews et al., 2017), lower rates of cancer screening (Anderson et al., 2013; Bennett et al., 2011), higher incidence rates of potentially preventable cancers (Henley et al., 2017; Zahnd et al., 2018b), more advanced stage at cancer diagnosis (Williams et al., 2016; Zahnd et al., 2018a), treatment that is less concordant with guidelines (Camacho et al., 2017; Zahnd et al., 2018c), low enrollment in clinical trials (Zullig et al., 2016), and higher mortality rates (Blake et al., 2017; Hashibe et al., 2018; Moy et al., 2017).

Researchers increasingly advocate the use of multilevel (or hierarchical) modeling to evaluate rural cancer disparities (Blake et al., 2017; Meilleur et al., 2013). Multilevel analytical approaches allow for the simultaneous examination of at least two levels of data. For example, this may include individuals (level I) nested or grouped by census tract or county (level II). For many cancers, individual characteristics such as race/ethnicity, gender, or age strongly influence cancer risks and disparities. However, characteristics of an individual's *context* may also play a role. Context as defined by MacIntyre and colleagues, comprises "opportunity structures in the local physical and social environment" (Macintyre et al., 2002). The physical environment consists of physical features of an area (e.g. water and air quality), built environment (e.g. sidewalks, recreation facilities), and available/accessible health services (Macintyre et al., 2002). The social environment encompasses socioeconomic conditions, occupational opportunities, social interactions and resources, and other health-related attributes of the places where people live and work (Macintyre et al., 2002). For the purpose of this paper, context/contextual variables will refer to group- and area-level characteristics (e.g. area-level poverty or residential segregation) that influence health outcomes (Diez Roux, 2002; Meilleur et al., 2013)

From a statistical perspective, utilization of multilevel modeling techniques to examine the effect of rurality on health outcomes may have advantages over either traditional regression or ecological analyses. Meilleur and colleagues refer to multilevel modeling as "ideal statistical approach" for the purposes of evaluating rural cancer outcomes (Meilleur et al., 2013). Multilevel modeling approaches account for the non-independence of observations within groups (e.g. geographies) which enables more accurate calculation of standard errors and subsequent reduction in the opportunity for Type I errors (Diez-Roux, 2000). The hierarchical structure of these models enables researchers to evaluate the effects of individual-level variables, group (place) level variables, and the cross-level interactions on

health outcomes (Wang et al., 2012). This may be particularly germane to the study of rural cancer outcomes because rural areas have varying place and population characteristics that affect cancer-related exposures, risk behaviors, and access to diagnosis and treatment services (Probst et al., 2004).

Our paper is also motivated by the growing use of multilevel modeling in cancer studies (Arcaya et al., 2016; Zahnd and McLafferty, 2017). A recent systematic review found that, over the past 15 years, multilevel modeling has been used in analyzing many types of cancer data including registry, cohort, clinical trial, administrative, hospital system, and clinical surveillance data across all cancer types and across all areas of the cancer control continuum (Zahnd and McLafferty, 2017). Despite its conceptual and statistical advantages, multilevel modeling has been underutilized in the study of rural cancer disparities (Meilleur et al., 2013). A commentary from the National Cancer Institute (NCI)'s Division of Cancer Control and Population Sciences stated: "more work is necessary to disentangle the effects of individual-level [socioeconomic status] and area-level factors (e.g. census tract poverty) in multivariable, multilevel models to understand the independent association of rurality on outcomes related to cancer prevention and control" (Blake et al., 2017). To guide understanding of rural cancer disparities and respond to the NCI's call, it is important to develop a conceptual framework for multilevel analyses and to evaluate the distinctive contributions and challenges of multilevel modeling for cancer control research within rural contexts (National Cancer Institute and Science, 2018). In order to better inform the implementation of such strategies, it is imperative to appropriately conceptualize rural context. The Cancer Prevention and Control Research Network (CPCRN) seeks to address this imperative. The CPCRN is a network of academic, public health, and community partners that aims to reduce the burden of cancer of underserved populations, such as those living in rural areas, through adoption of implementation of evidence-based cancer prevention and control strategies (Cancer Prevention and Control Research Network, 2019).

Our goal is to present a conceptual framework for understanding rural cancer disparities and to discuss both challenges and opportunities in using multilevel modeling to investigate rural cancer disparities. We argue that for rural populations, interlocking social, environmental, and health care factors that exist at multiple scales strongly influence cancer risks and outcomes. We characterize these factors as: micro, macro, and supra-macro factors according to the scale of influence (Table 1). In the next section, we discuss the opportunities and challenges of multilevel statistical modeling in rural cancer research in the United States.

2. Development of a conceptual framework

We constructed a conceptual framework to guide the inclusion of rurality and other factors that may have an effect across the cancer control continuum in multilevel analyses of cancer in rural populations (Fig. 1). We anticipate that such a framework would be applied to analysis of relative disparities in which urban populations would serve as the reference group. The National Cancer Institute recommends that the hypothesized "best off" group (i.e. urban) be the reference group in analysis (Harper and Lynch, 2005). However, we have designed this conceptual framework to be flexible across geographic definitions and units.

Practically, such a framework may be especially useful for analysis of secondary data from cancer registries, administrative databases, population-based surveys, health system records, and cohort studies where there is likely greater opportunity to link individual-level data to area-level data at the county, census tract, or other geographic levels. This framework also may be useful to conceptualize prospective data collection in multilevel interventions, which is an increasingly recommended approach to address rural cancer disparities, that may be implemented at the individual and community levels (Kennedy et al., 2018; Wheeler and Davis, 2017).

This framework incorporated several well-cited and utilized models, frameworks, and reviews (Table 1). The Model for Analysis of Population Health and Health Disparities developed by Warnecke and colleagues serves as the foundation for our framework (Warnecke et al., 2008). Warnecke's Model defines factors affecting health disparities as either proximal, intermediate, or distal to individual-level outcomes and was identified by Lynch and Rebbeck as the most appropriate multilevel framework for assessing cancer disparities as an outcome (Lynch and Rebbeck, 2013; Warnecke et al., 2008). Further, Warnecke's model has been used as a multilevel intervention framework to address rural cancer disparities (e.g. the Geographic Health Equity Alliance's Multi-Level Framework) (Weaver et al., 2016). Cancer disparities can occur across the continuum, characterized by the progression of disease from etiology to survivorship and mortality, which we describe by considering both the National Cancer Institute's Cancer Control Continuum and Wingo's Framework for Cancer Surveillance (National Cancer Institute, 2017; Wingo et al., 2005).

To use nomenclature more common in multilevel statistical modeling, we have characterized factor groupings as either micro, macro, or supra-macro factors, respectively (Arcaya et al., 2016; Duncan et al., 1998; Cromley and McLafferty, 2012). The factors delineated within each grouping in our framework met two criteria. First, all factors were broadly characterized by well-cited, established conceptual frameworks and/or definitions from seminal articles in the field of health disparities. Second, all factors had either been considered in previous studies that used multilevel modeling methods in geographic contexts or have been identified as factors particularly pertinent to rural health disparities that have been used in traditional regression or ecological studies (Table 1). Micro-level factors were characterized broadly as individual demographics and risk factors, drawing from Warnecke's Model. Individual demographics were further characterized based upon how those demographic characteristics either *enable* individuals to utilize health care services or *predispose* them to a need for health care services in accordance with the Aday and Anderson Framework for the Study of Access (Aday and Andersen, 1974). To characterize macro factors, we drew upon other Warnecke's model components, Khan's Typology of Access, and Krieger's Domains of Social Inequality to characterize the factors relevant to rural contexts—specifically the effects of social and physical environment as well as spatial and aspatial access to care in rural populations (Khan and Bhardwaj, 1994; Krieger, 2005; Warnecke et al., 2008). Supra-macro factors are broadly conceptualized as the policy and systems environment that may affect cancer across the continuum as characterized by frameworks from Taplin and Mobley (Mobley et al., 2014; Taplin and Rodgers, 2010).

3. Cancer control continuum

We characterized the cancer control continuum by utilizing frameworks from the NCI and Wingo (Fig. 1) (National Cancer Institute, 2017.; Wingo et al., 2005). The NCI's framework considers the effect of cancer on individuals and populations as an overlapping progression of the disease and how it can be controlled: etiology, prevention, detection, diagnosis, treatment, and survivorship. Wingo's Framework similarly considers cancer across the continuum: healthy populations, new diagnosis of cancer, treatment of cancer, living with cancer, and dying of cancer, but also discretely places each construct as part of either primary, secondary, or tertiary prevention of cancer. We merged constructs from each framework to delineate the relationship between disease progression and levels of associated prevention.

4. Micro-level factors

4.1. Enabling and predisposing factors

Micro-level factors (i.e. individual factors), such as demographic characteristics, health behaviors, occupational exposures, and genetic characteristics, may affect disparities along the cancer control continuum. In most multilevel models, micro-level factors comprise the individual level I variables. Particularly germane for rural disparities research and subsequently our conceptual framework, micro-level characteristics may enable or predispose an individual's access to care, as characterized by Aday and Andersen's Framework for the Study of Access (Aday and Andersen, 1974). Insurance status, marital status, and socioeconomic factors are enabling factors in that they are a "means" to accessing services. Factors like age, sex, and race/ethnicity may predispose an individual's access to care/propensity to utilize healthcare services. The enabling and predisposing factors have been shown in previous studies to affect cancer outcomes along the continuum. (Aizer et al., 2013; Cook et al., 2009; Ellis et al., 2017; Unger et al., 2013). It is important to understand how t individual-level factors may affect cancer outcomes within rural geographic contexts, particularly as rural residents face unique challenges in access to cancer care including less availability of cancer treatment, transportation barriers, higher rates of uninsured status, and less access to clinical trials (Charlton et al., 2015).

4.2. Genetic and non-modifiable risk factors

In addition to the effect of individual factors on health care utilization, some demographic factors (i.e. age, race/ethnicity, and sex), as well as genetics, are non-modifiable risk factors for development of cancer. Genetic factors influence cancer risk and responsiveness to treatment. For example, since the passage and implementation of the Affordable Care Act, utilization of BRCA testing has increased among all at-risk women, but the magnitude of this increase differs between rural and urban women (Kolor et al., 2017). With the increase of genetic testing modalities and the increased coverage of testing because of the Affordable Care Act and recent Medicare regulations, micro-level genetic factors may become increasingly important to consider within the rural-urban dynamic, not necessarily because rural-urban genetic differences are anticipated, but because rural-urban differences in *known* genetic risk (due to testing differences) may be anticipated. Further, non-modifiable,

individual-level risk factors may interact with macro-level factors, which underscores the importance of considering area-level factors in conjunction with individual-level factors in multilevel models. For example, one study found that residential segregation differentially affected rural African Americans' and rural Hispanics' utilization of cervical cancer screening (Caldwell et al., 2017). It is important to note, also, that although race and ethnicity are often individual-level variables within datasets, race and/or ethnicity is often not an intrinsic risk factor for greater cancer risk, lower screening or treatment utilization, and/or poorer cancer outcomes. Rather, racial disparities in cancer may be due to actual and perceived racial biases and discrimination within the health care system and systemic racism (Rathore and Krumholz, 2004). Thus, although it is an individual-level factor, the association that race and ethnicity may have with a cancer outcome may be due more to the social and health care context.

4.3. Modifiable risk factors

Particularly relevant to the etiology of cancer are behavioral risk factors that are often more common in rural populations in aggregate (e.g. smoking, obesity) or occupational or environmental exposures that may differ between rural and urban contexts (e.g. agricultural and industrial exposures, respectively) (Dasgupta et al., 2012; Doogan et al., 2017; Patterson et al., 2004). Researchers can explore how those individual behavioral and/or occupational risk factors, if available within a dataset of interest (e.g. datasets from hospital systems or cohort studies), may affect cancer outcomes for individuals within rural-urban contexts. For example, previous multilevel studies have considered individual level occupation and contextual geographic remoteness (i.e. rurality) and their effects on breast cancer survival (Dasgupta et al., 2012).

5. Macro-level factors

Macro-level factors will often be the Level II factors that characterize an individual's geographic context (e.g. census tract, zip code, county) in multilevel models. Macro-level factors are characterized by social and physical context (Fig. 1) (Warnecke et al., 2008). Social context can include area-level socioeconomic measures such as poverty level, median household income, racial residential integration, and social capital (Warnecke et al., 2008). Physical context includes accessibility and availability of health care services and the built environment, which includes access to health-promoting services (e.g., farmers' markets) or conversely, health inhibiting resources (e.g., fast food restaurants) (Gomez et al., 2015). To further define and characterize social and physical context, we considered Krieger's Domains of Social Inequity and Khan's Typology of Access as well as measures identified in review papers by Gomez and Colditz (Table 1) (Colditz and Wei, 2012; Gomez et al., 2015). Krieger's domains of social inequity—at a contextual level—include elements of socioeconomic position and race/ethnicity (i.e. socioeconomic status and racial integration) (Krieger, 2005). Similarly, Khan's typology of healthcare access characterizes aspatial access as the social, economic, political, or cultural barriers or facilitators to health care access (Khan and Bhardwaj, 1994).

5.1. Social context

Characteristics of social context may affect the risk of developing cancer, the ability to access necessary health care services to prevent or treat cancer, and the risk of cancer-related death. Indeed, socioeconomic characteristics are the most commonly used contextual factor in multilevel analyses of cancer outcomes (Zahnd and McLafferty, 2017). Other commonly used characteristics of social context focus on the racial/ethnic distribution of a geographic area, including crude measures of racial composition (e.g., percent non-White) and derived measures of residential segregation (e.g. Massey's isolation index), and socioeconomic deprivation (e.g. Townsend deprivation index and Area Deprivation Index) (Massey and Denton, 1988; Singh, 2003; Townsend, 1987; Zahnd and McLafferty, 2017). These measures are particularly important for the exploration of rural cancer disparities. Rural populations tend to be older and poorer than urban populations, but the context of rural or urban poverty may uniquely affect cancer outcomes. Similarly, the effect of racial composition or area-level segregation may distinctively impact health outcomes in rural compared to urban minorities, or in rural white compared to rural minority populations (Caldwell et al., 2017; Probst et al., 2004). Social capital, another measure of social context, can be characterized as the community value experienced from social networks, norms, and trust and may affect health differently in rural and urban areas due to the different population sizes and different cultural norms (Yen and Syme, 1999). For example, although not explicitly cancer-related, one multilevel study suggested that in urban populations high social capital was associated with higher odds of smoking during pregnancy, while high levels of social capital in rural areas were associated with lower odds of smoking during pregnancy (Shoff and Yang, 2013).

5.2. Physical context

Physical context is characterized by access to health care services, health-promoting resources, and health inhibiting features, as well as area-level environmental exposures. Access to healthcare services (e.g. area-level travel distance; provider density ratios) is an especially important measure of physical context and has been used in some studies as a proxy measure for rural status (Meilleur et al., 2013; Zahnd and McLafferty, 2017). Access can be further characterized as potential and realized accessibility (Khan and Bhardwaj, 1994). Potential access is the relative availability of health care services relative to population-level need. Studies employing multilevel models to evaluate cancer outcomes have used a myriad of measures of potential access, most frequently using provider-population ratios, spatial filtering measures (e.g. two-step floating catchment area), or travel distance measures (Khan-Gates et al., 2015; Zahnd and McLafferty, 2017). Realized access is the actual utilization of services and may be characterized in multilevel models as, for example, the area level utilization of cancer screening services (% of Medicare beneficiaries up-to-date with cancer screening recommendations) (Mobley et al., 2015). Health promoting resources and health inhibiting features (i.e. built environment) are also important measures of physical context that may differ between rural and urban areas and subsequently have varying effects on cancer outcomes. Health promoting resources considered in previous multilevel studies have included resources such as access to parks and farmers' markets while health inhibiting features have included alcohol outlet, fast food, and tobacco retail densities (Keegan et al., 2014; Levin et al., 2014; Major et al., 2014; Shariff-Marco et al., 2017). Area-level environmental exposures considered in multilevel cancer studies have

included UV radiation and air pollution exposures (Jerrett et al., 2005; Richards et al., 2011). Previous studies have shown that rural populations have less access to health promoting resources such as parks (Wen et al., 2013). Similarly, rural and urban areas may vary in types of environmental exposures. For example, rural areas tend to have better air quality, but poorer drinking water quality compared to urban areas (Strosnider et al., 2017).

5.3. Rural-urban status

Rural-urban status as an independent characteristic, however, is not bound by the definitions of either social or physical context and certainly spans both contexts. Krieger identifies rural-urban status as a domain of social inequality, and Khan characterizes aspatial access as social, economic, political or cultural barriers/facilitators to care, which will be unique to rural or urban contexts and independent of other contextual measures (Khan and Bhardwaj, 1994; Krieger, 2005). There is no consensus on what constitutes "rural", either qualitatively or quantitatively. In fact, there are at least 15 federal definitions of rurality (Blake et al., 2017). However, definitions of rural in health policy and research tend to be driven by the foci of federal agencies, the specific research questions posed by researchers, and the geographic scale of available data (Hart et al., 2005). While different measures have been used, the commonality of how "rural" is defined is by small population size and geographic isolation. In most multilevel studies, rural-urban status has primarily been defined by federal agency measures from the United States Department of Agriculture (USDA), U.S. Census Bureau, or Office of Management and Budget definitions (Zahnd and McLafferty, 2017). USDA measures that characterize counties (Rural-Urban Continuum Codes and Urban Influence Codes) or census tracts (Rural-Urban Commuting Area (RUCA) codes, which can also be approximated to zip codes) are most commonly used. These USDA measures take into consideration population size within a geographic area, proximity to metropolitan areas, and commuting patterns. Several researchers have suggested that, if data are available at the appropriate geographic scale, census tract RUCA codes may be the best rural-urban measure for cancer research because it considers both population density and a component of travel distance (Meilleur et al., 2013; Pruitt et al., 2015).

Further, rural populations are not racially, ethnically, nor socioeconomically monolithic. One in five rural Americans is a person of color, and in some rural areas, the population is greater than 50% black, Hispanic, Asian, Native American, Native Hawaiian or some combination of racial/ethnic minority (Housing Assistance Council, 2012; Lichter, 2012; Probst et al., 2004). While rural areas tend to be poorer, there are some rural areas that are quite affluent. Populations in "amenity-rich" rural areas have grown 20% between 1990 and 2015 (Ulrich-Schad and Duncan, 2018). The sociodemographic diversity of rural America stresses the need to simultaneously consider rural-urban status, socioeconomic factors, and racial/ethnic composition in multi-level studies of cancer outcomes.

6. Supra-macro level factors

Supra-macro factors are characterized by both policies and systems that affect cancer outcomes and may be particularly important to elucidate disparities beyond what is measured at the micro or macro levels (Bambra et al., 2019). These will often be the Level II

or III factors in multilevel models insofar as they describe the larger geographic context (e.g. state or region) in which a rural county or census tract is nested (Fig. 1). Supra-macro factors are rarely considered in multilevel analyses of cancer outcomes despite the fact that they may have the largest population-level health impacts. (Frieden, 2010; Zahnd and McLafferty, 2017). We drew from Taplin and Mobley's works to delineate these policies and systems as the state and federal level policies related to insurance coverage policies, hospital performance, and facility/provider regulations and how these may uniquely impact cancer diagnosis, treatment, and survival in rural populations (Table 1) (Mobley et al., 2014; Taplin and Rodgers, 2010).

6.1. Health policy

State-level health care policies may be important to include in multilevel models, especially to examine how policy affects cancer outcomes differently across rural-urban contexts. In Fig. 1 and Table 1, we delineate health policies related to insurance and public health policies as well as provider and facility regulations. A particularly salient example is that Medicaid expansion has been less likely to occur in states with large rural populations (Foutz et al., 2017). Studies have explored the impact of Medicaid expansion on cancer screening, staging, treatment and mortality-incidence ratios, but rural-specific and rural-urban comparisons have yet to be explored (Ajkay et al., 2018; Choi et al., 2015). Further, broader social and public health policies may disproportionately affect rural populations. For example, Doogan and colleagues posit that the widening disparity between rural and urban smoking rates may be because state-level tobacco control policies are disproportionately less effective due to lack of cultural relevance and/or poor implementation and enforcement in rural areas (Doogan et al., 2017). At the local level, rural areas may also be less likely to have smoking-related regulations (e.g. indoor smoke-free bans).

6.2. Policy-relevant contexts

Policy relevant contexts like the four federal regional designations may be an important supra-macro factor to consider (Boyd, 2006). These multi-state or multi-county regions have been legislatively designated for socioeconomic development purposes. The two largest federally designated regions include the Appalachian Regional Commission and the Delta Regional Authority—both largely rural regions with stark cancer disparities may be particularly relevant (Wilson et al., 2016; Zahnd et al., 2017). Inclusion of these designations in multilevel models has implications for federal resource allocation and interventions. For example, the Appalachia Community Cancer Network is an NCI-funded network addressing cancer disparities in Appalachia through community-based participatory research approaches. (Appalachia Community Cancer Network, n.d.). Multilevel modeling approaches may be an effective way to evaluate the impact of these efforts on cancer outcomes in network communities compared to non-network Appalachian communities by also accounting for relevant micro- and macro-level factors.

7.   Additional considerations for multilevel analysis of rural cancer outcomes

By integrating previously published frameworks, models, and reviews, we developed a conceptual model for how cancer disparities could be considered within a rural context utilizing multilevel modeling approaches. Our model considered factors at the micro, macro, and supra-macro level that may affect outcomes across the cancer control continuum and described specific constructs within each level. Of note, our model delineated how rural-urban status spans social and physical contexts and may affect cancer outcomes independent of other area-level characteristics. With the increasing call for the utilization of multilevel modeling approaches in the evaluation of rural cancer outcomes, this model can provide guidance for epidemiologists, health service researchers, geographers, and sociologists doing quantitative rural cancer research. However, we also posit that there are additional methodological considerations that should be considered, as described below.

7.1.   Addressing multicollinearity among contextual variables

A challenge when considering multiple contextual variables within a multilevel model is that of multicollinearity, particularly among highly correlated variables like socioeconomic factors (e.g. area-level poverty, educational attainment, etc.) that also may be collinear with rural-urban status. There are several ways to address this. For example, some studies may use a single socioeconomic variable like area-level poverty, which has been identified as the most robust area level socioeconomic factor relating to cancer incidence (Krieger et al., 2002).

Other studies utilize multiple socioeconomic variables to develop a single composite variable (e.g. Area Deprivation Index). Some studies utilize data reduction approaches like principal component analysis, which creates a smaller number of index (component) variables from a larger number of variables, and factor analysis which creates latent variables that cannot be directly measured from individual variables. For example, Belasco and colleagues have used rural-urban status in conjunction with socioeconomic variables to develop a health care accessibility index using principal component analysis to evaluate rural cancer-related behaviors and outcomes. (Belasco et al., 2014). In another example, McLafferty and colleagues used factor analysis to consider how different factors (e.g. socioeconomic disadvantage, socioeconomic barriers, high healthcare needs) in conjunction with rural-urban status affect breast cancer staging (McLafferty et al., 2011).

7.2.   Cross-level interactions

One of the strengths of multilevel modeling is the opportunity to explore cross-level interactions between area-level and individual-level characteristics. The interaction between race and rural-urban status is an important example (Probst et al., 2004). Racial and ethnic minorities comprise 20% of rural populations overall, and the populations of some rural areas are majority black, Hispanic, or other racial/ethnic minority population (Housing Assistance Council, 2012; Lichter, 2012). It is important to consider how rural context may affect cancer outcomes in these populations, especially as rural minorities may experience disparities in cancer screening, incidence, and staging both compared to rural whites and

urban minorities (Caldwell et al., 2016; Zahnd et al., 2018a; Zahnd et al., 2017). There is an increasing call for the consideration of the intersection between individual levels like race and ethnicity and the context of "social identity"(Green et al., 2017) of which rural-urban status could arguably be defined as a construct. Consideration of cross-level interactions in multilevel regression models provides an analytical application of conceptual intersection of individual factors and rural context.

7.3. Cross-classified models

While area-level characteristics of where one lives (e.g. level of rurality, poverty, access to care, etc.) may help explain cancer outcomes, other contexts independent of geography may also play a role. For example, characteristics of where one receives care may also affect cancer outcomes—particularly when it comes to screening and treatment. To appropriately consider the independent effects of overlapping contexts, such as place-based (e.g. county of residence) and clinical (e.g. hospital where treatment was received) contexts, cross-classified models can be utilized. An additional strength of the cross-classified models is that the consideration of overlapping contexts reduces biases in standard errors and subsequently the likelihood of Type I errors (Meyers and Beretvas, 2006). Previous studies have included hospital characteristics like number of beds, teaching hospital status, and surgical volume in cross-level models to evaluate cancer outcomes (Ratnapradipa et al., 2017; Schootman et al., 2014a, 2014b). Salient to the exploration of rural cancer outcomes, additional hospital characteristics (e.g. rurality of hospital, critical access status) may be important to consider in cross-classified models.

7.4. Spatial dependence concerns

Multilevel models often use administrative units, such as county, zip code, or census tract, as their grouping variable at the macro and supra macro levels. While indeed such units are intuitive and useful for linking area-level data on sociodemographic characteristics, standard multilevel models do not consider geographic proximity or spatial dependence among "neighboring areas." Instead they regard each area (e.g. county, zip code, or census tract) as independent of each other (Owen et al., 2015). In reality, "spillover" occurs, as adjacent or nearby geographic areas outside of one's location of residence may have an impact on individual cancer outcomes. To address these concerns, more complex modeling techniques can be implemented. For example, conditional and spatial autoregressive models can consider both the multilevel structure and spatial dependence of data to evaluate health outcomes like cancer (Arcaya et al., 2012; Dong and Harris, 2015). This enables geographic membership (i.e. place) and spatial location (i.e. space) to be simultaneously assessed.

7.5. Small area estimation approaches

Thus far, we have primarily discussed the use of multilevel modeling to appropriately consider the effect of rural context on individual cancer outcomes. However, multilevel modeling in small area estimation (SAE) techniques is also useful to estimate rates of cancer-relevant health behaviors, cancer screening, and cancer mortality rates within small areas like rural counties (Berkowitz et al., 2018; Eberth et al., 2013, 2018; Mokdad et al., 2017). By developing indirect estimates using multilevel modeling techniques, including the aforementioned conditional autoregressive modeling approaches, SAE can address concerns

of unstable rates that are produced when sample sizes are small. These techniques are particularly useful for estimation of rates in more sparsely populated, isolated rural areas. SAE indirectly estimates rates for small areas by borrowing information from population-based estimates (e.g. from population-based surveys like the Behavioral Risk Factor Surveillance System survey and the National Health Interview Survey) under the assumption that areas with similar characteristics will have similar outcomes (Raghunathan et al., 2012). Further, spatially explicit SAE techniques are especially powerful as they draw information from adjacent areas to help account for spatial dependence. Practically, SAE approaches can provide important information for public health surveillance, subsequently informing policy development and resource allocation.

8. Conclusions

Multilevel modeling is a conceptually meaningful and statistically robust approach to analyzing rural cancer outcomes across the cancer control continuum. Our conceptual framework can serve as a guide for researchers developing models to examine the independent contribution of rural-urban status on cancer outcomes in epidemiological, health services, geographic, and sociological studies, while also accounting for other important micro, macro, and supra-macro factors. In addition to integrating our proposed framework, researchers should consider specific methodological concerns relevant to potential collinearity of model predictive variables, structure (i.e. cross-level interactions and cross-classified models), and spatial dependence when exploring cancer outcomes relative to geographic membership.

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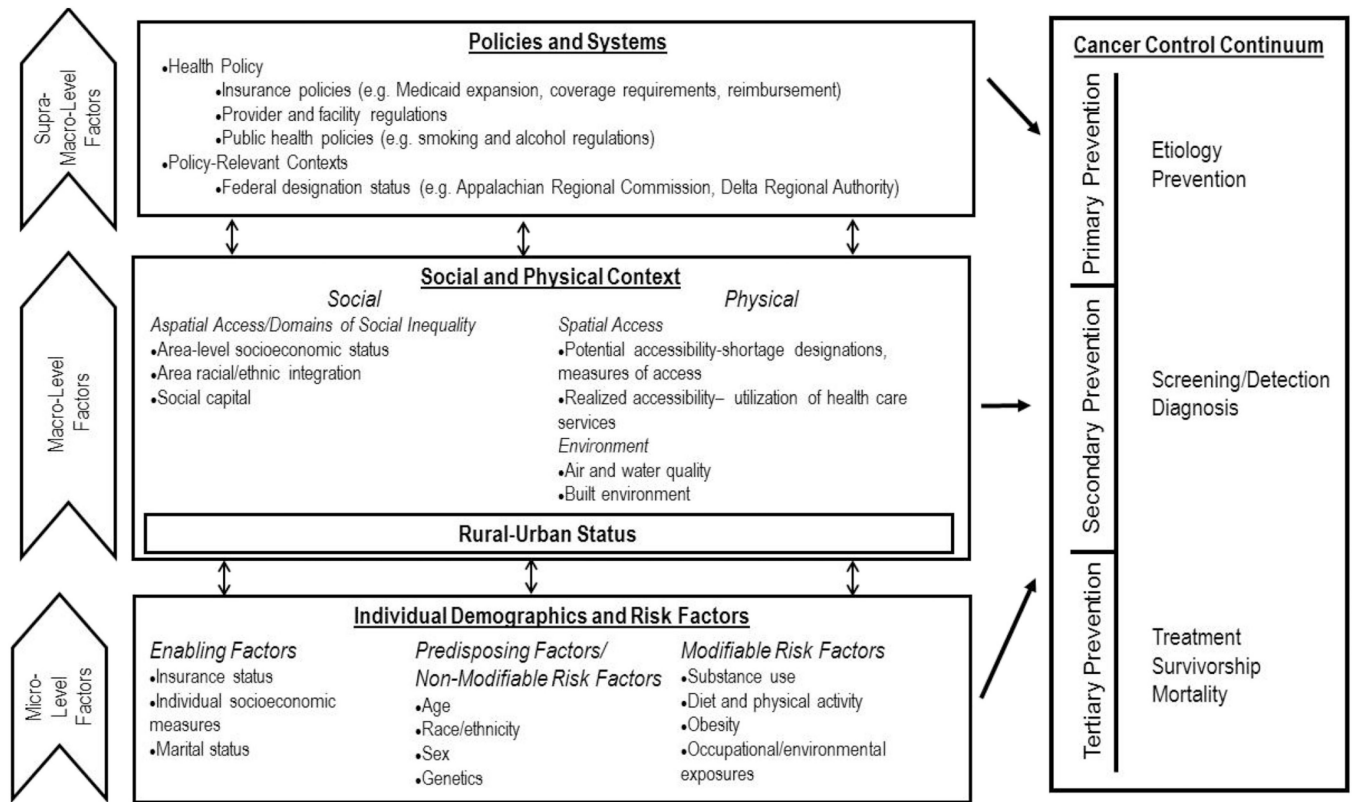
Fig. 1.
Conceptual model for multilevel analysis in rural cancer control.

Table 1

Description and rationale for components of the model for the multilevel analysis of rural cancer control in the United States.

Level or outcome	Framework, model, or review	Components of framework, model, reviews incorporated into conceptual framework	Rationale for inclusion
Level			
Foundational framework	Warnecke's Model for Analysis of Population Health and Health Disparities (Warnecke et al., 2008)	• Multilevel structure ○ Proximal (micro)-level factors inclusive of individual demographics and risk factors ○ Intermediate (macro)-level factors-inclusive of both physical and social context ○ Distal (supra macro)-level factors-inclusive of policy impact	Identified as the most appropriate multilevel framework to evaluate cancer disparities (Lynch and Rebbeck, 2013)
Micro-level factors	Aday and Andersen's Framework for the Study of Access (Aday and Andersen, 1974)	• Enabling factors-enable individuals to utilize health care services • Predisposing factors-predispose factors to need health care services	Details how individual level factors may affect access to health care and subsequently impact cancer outcomes
Macro-level factors	Khan's Typology of Access (Khan and Bhardwaj, 1994)	• Distinctions between aspatial (social) and spatial (physical) access to health care services • Distinctions between realized and potential access to health care services	Expands upon Warnecke's characterization of physical context as inclusive of the availability and accessibility of health care
	Krieger's Domains of Social Inequality (Krieger, 2005)	• Specific social factors that contribute cancer disparities across the cancer continuum	Provides social factors that affect cancer outcomes that may be independent of social factors that affect access to health care services noted by Khan
	Gomez et al. review of the impact of neighborhood social and built environment factors across the cancer continuum (Gomez et al., 2015)	• Review of specific measures of physical context (e.g. built environment) that may affect cancer across the cancer control continuum	Expands upon Warnecke's characterization of physical context as inclusive of the built environment
	Colditz et al. review of the biologic, social, and physical environment on cancer mortality (Colditz and Wei, 2012)	• Summary of specific measures of physical context (e.g. air and water environment) that may impact cancer outcomes	Expands upon Warnecke's characterization of physical context as inclusive of the environmental factors like air and water quality
Supra macro-level factors	Taplin's Multiple Layers of Influence in the Cancer Care Continuum (Taplin and Rodgers, 2010)	• Delineation of specific factors of the health policy environment that may, in particular, affect cancer care	Provides specificity to the broad, supra-macro characterization of the "health care system" by Warnecke
	Mobley's Socio-ecological model of breast and colorectal cancer screening utilization (Mobley et al., 2014)	• Specification of insurance and provider regulations at a "supra-macro" level (i.e. state) that may affect cancer screening	
Outcomes			
Cancer control continuum	NCI's Cancer Control Continuum (National Cancer Institute, 2017)	• Delineation of the specific stages in the cancer-process in which populations may experience disparities and in which health care and public health professionals may intervene	Characterizes a disease-specific area of health disparities that are affected by multilevel factors
	Wingo's National Framework for Cancer Surveillance (Wingo et al., 2005)	• Outlines the process of cancer's effect on individuals and populations in the context of primary, secondary, and tertiary prevention	