

MODELING GEOGRAPHIC BARRIERS TO OVARIAN CANCER CLINICAL TRIALS IN PENNSYLVANIA

Moira Conway

Department of Geography
Kutztown University of Pennsylvania

Diana Malandruccolo

Department of Public Health
Arcadia University

Jennifer Hinkel

Centre for Evidence Based Medicine
University of Oxford

Abstract

Although clinical trials offer the best management of cancer patients according to National Comprehensive Cancer Network, patient participation in trials remains low. Multiple barriers to trial participation exist; one barrier documented in the literature is geographic. This barrier may present a greater hurdle for cancer patients in rural areas. We assess geographic accessibility to oncology treatment trials through a state and county-level lens in one state (Pennsylvania) and one tumor type (ovarian cancer), applying a methodology replicable to other states and disease areas. GIS methods are used to map and rank counties based on four variables. These were combined to determine each county's overall vulnerability. Results from the suitability analysis show that the most vulnerable counties are rural. Quantifying geographic and socio-economic hurdles to clinical trial participation may illuminate potential changes to policy or practice that could improve rural access. Counties with vulnerability can be targeted for intervention.

Background

Patient participation in clinical trials advances scientific research; in the case of cancer, participation in either the standard of care (control) arm or intervention arm of a clinical trial has also been indicated to have survival benefit for participating patients in the first year after cancer diagnosis (Unger et al., 2014). However, relatively few patients diagnosed with cancer go on to participate in clinical trials. A 2018 report from the American Cancer Soci-

ety (2019) showed that, "Most patients express a willingness to participate in clinical research, yet only a small fraction ultimately end up enrolling in a cancer clinical trial due to barriers that make participation difficult or even impossible. Consequently, approximately 20% of cancer clinical trials fail due to insufficient patient enrollment." This trend persists despite the existence of clinical practice guidelines encouraging trial participation; according to the National Comprehensive Cancer Network (NCCN), which publishes such guide-

lines, “the best management of any cancer patient is in a clinical trial” (Galsky 2015).

As clinical trials are pivotal in the advancement of oncology care, high enrollment rates are crucial to evidence generation regarding cancer management and treatment at a population level. Continued low enrollment in clinical trials limits generalizability of the results (Carey et al. 2017). A first step in exploring clinical trial participation is examining their geographic accessibility to patients vulnerable to cancer.

Trial participation may be perceived as having even greater value for evidence generation and potential patient benefit in diseases with high unmet need and fewer treatment options. Ovarian cancer is one such disease, not only because it is often diagnosed at an advanced stage, but because treatment options are limited and even patients who respond to initial therapy have a high probability for relapse and eventual death (Guarneri et al. 2010; Herzog and Monk 2017).

Using the state of Pennsylvania as a case study, we examine accessibility to ovarian cancer trials. We seek to explore how geographic difference may impact accessibility to such trials, and we consider how accessibility or lack thereof may affect trial participation for patients diagnosed with this disease.

Literature Review

Although it has been frequently explored, the rate of enrollment in oncology clinical trials has not varied much over time. As opposed to only

looking at patient barriers, Unger et al. (2019) analyzed 13 studies with 8,883 patients to determine structural and clinical barriers to clinical trial participation. Structural barriers included accessibility of the trial to the patient and whether there was a trial available at their local health or academic institution. Clinical barriers included inclusion and exclusion criteria for patient participation in the trial. Results showed that clinical trial participation is unachievable for over 75% of cancer patients due to accessibility, patients being ineligible, and non-enrollment (Unger et al. 2019). With the majority of cancer patients not being able or willing to enroll in clinical trials, diversity in clinical trials is often lacking.

Diversity in clinical trial enrollment is key to producing findings that are generalizable, yet patient diversity in cancer clinical trials remains a persistent challenge, particularly in the gynecologic malignancies. Mishkin et al. (2016) looked at 18,913 National Cancer Institute-sponsored ovarian, uterine, and cervical oncology trials between 2003 and 2012 to evaluate the demographics of the trials compared to the incident US patient population. Overall, ovarian cancer trials were the least diverse in terms of race, age, and ethnicity, with African-American and Hispanic women being the most underrepresented. Underrepresentation in ovarian cancer research is especially an issue as African American women are disproportionately affected by ovarian cancer. While incidence is higher in white women, African American

women experience higher mortality rates (Srivastava et al. 2017). Bristow et al. (2014) identified 11,770 advanced stage ovarian cancer patients and found that only 45.4% were being treated according to NCCN guidelines. African American patients, patients of low socioeconomic status, and patients living further than 80km/50mi from a high volume hospital experienced the highest levels of treatment that was not concordant to NCCN guidelines recommendations for oncology care. When analyzing the impact of geographic location to care that was concordant with NCCN guidelines, results showed that white patients were significantly more likely to travel for care than patients of other racial groups. Overall, geographic barriers to ovarian cancer treatment disproportionately affected women of low socioeconomic status and racial minorities (Bristow et al. 2014). These findings could play a role in why some groups are disproportionately affected by cancer and its effects.

Potential barriers to low clinical trial enrollment have been explored in the literature. Galasky et al. (2015) extracted metastatic breast, prostate, colorectal, and non-small cell lung cancer clinical trial location data from ClinicalTrials.gov to analyze potential geographic barriers to oncology clinical trials. A total of 227 trials with 5,011 sites were included. MapPoint 2013, a mapping software, was then used to determine the distance from each US zip code to the nearest clinical trial. Results showed that “45.6%, 50.2%, 52.2%, and 38.4% of patients with metastatic breast,

prostate, colorectal, and non-small cell lung cancer, respectively, would need to drive more than 60 minutes 1 way to access a clinical trial site” (Galasky et al. 2015). The longest travel times were located in the Mountain, West North Central, and West South Central regions. These findings indicate that oncology clinical trials in the United States lack geographic accessibility for significant numbers of the potentially eligible patient population. This could be due to the fact that trial sites are often chosen based on investigator location as opposed to patient location (Galasky et al. 2015). Similarly, Seidler et al. (2014) analyzed the geographic distribution of clinical trial sites in the United States as well as reasons for clinical trial site selection. 174,503 clinical trial sites were analyzed and compared by their location and spatiality. Results showed that clinical trial site locations were highly clustered around urban areas, with Seidler et al. (2014) concluding that this may be a reason that patients in rural areas are underrepresented in clinical trials.

Gaps in Literature

National Institute of Health guidelines for inclusion in clinical trials was updated in 1993 to include women and racial minorities. However, rural populations still remain underrepresented and excluded from the guidelines of inclusion (Seidler et al. 2014). Geographic minority enrollment in clinical trials remains underexplored in the literature, with very limited data examining the relationship between geography and ovar-

ian cancer care access/survival (Bristow et al. 2014).

GIS Methods for Health and Cancer Research

In recent decades, Geographic Information System (GIS) methods have been employed to conduct spatial analysis in a wide variety of topics. While GIS methods have been used in research in public health, and specifically cancer, it has been limited. In a study of the general use of GIS in identifying trends for cancer surveillance, Sahar et al. (2019) recognized that the use of mapping tools allows for a simpler understanding of data analysis by consumers and stakeholders. In turn, stakeholders can identify trends in the data and apply these informed trends to potential policy strategies that help to reduce cancer burden.

This is exemplified by studies that focused on geographical areas and cancer burden. In an effort to explore cancer burden—along with variation of incidence among different geographic areas in Fars Province, Iran—Golie et al. (2013) utilized GIS to assess geographic patterns of cancer incidence as well as trends in patterns over a decade. While distribution of cancer incidence changed year to year, there was clear spatial autocorrelation. Similarly, using GIS, Hayran (2004) utilized the Pennsylvania cancer registry and population data from the National Center for Health Statistics to analyze prostate cancer incidence spatially over the state of Pennsylvania in order to identify targeted intervention techniques. Madhu

et al. (2016) analyzed breast cancer incidence in southern Karnataka, India, using GIS, and were able to conclude that urban areas were at higher risk although temporal data showed the potential for increased risk in urban areas. Authors recognized the greater benefit of GIS as a visual tool when compared to presenting data in tables and columns. Additionally, all studies reviewed recognized the implications that the results of their GIS analyses could have on potential interventions and/or policy makers.

Suitability analyses take GIS utilization a step further by qualifying and comparing varying factors to determine the most suitable site location for those factors, as seen in the following studies. In an effort to maximize healthcare coverage, minimize competition with surrounding healthcare units, and meet zonal health requirements, Mishra et al. (2012) used five accessibility and healthcare need factors in a suitability analysis. Authors concluded that findings from the suitability analysis, which determined the best locations for health care units, would be useful to policy makers and allocation of funds, which could ultimately improve health and quality of life. Case and Hawthorne (2013) similarly examined the accessibility of social services in Atlanta, Georgia, focusing on distance and transportation. A suitability analysis was done to help stakeholders visualize gaps in coverage and determine ideal locations for social service providers that can best meet the needs of the community. Finally, Ziaul and Pal (2016) used a suitability analysis to examine whether the exist-

ing distribution of water service centers is ideal for the unequal population distribution and varying growth of population in West Bengal. Using six factors, Ziaul and Pal (2016) determined the areas with the highest demand of water service centers. The suitability analysis studies that were reviewed shared a trend of using spatial and non-spatial data as well as focusing their results on meeting the needs of the community.

Another GIS method used to examine accessibility is a gravity model, particularly the Huff gravity model. This has been traditionally used for business applications, to examine probability of interaction from origin locations to potential store locations. This model has been adapted to examine public health applications, such as examining vulnerability to casino gaming (Doran and Young 2010; Conway, 2015). Luo (2014) used a Huff Model to analyze geograph-

ical access to primary care settings in Springfield, Missouri that reflected the impacts of distance and primary care site capacity. As this model relies heavily on distance, it can be adapted to examine accessibility to ovarian cancer clinical trials from population origins.

Methods

In order to determine difference in accessibility in varying geographies in Pennsylvania, the counties in Pennsylvania have been divided into two categories, urban and rural. The definitions have been created by the Center for Rural Pennsylvania and are based on population density using 2010 population data. Pennsylvania has an average of 284 persons per square mile. Counties above the average are considered urban, while counties below are considered rural (Center for Rural Pennsylvania, 2014) (Figure 1).

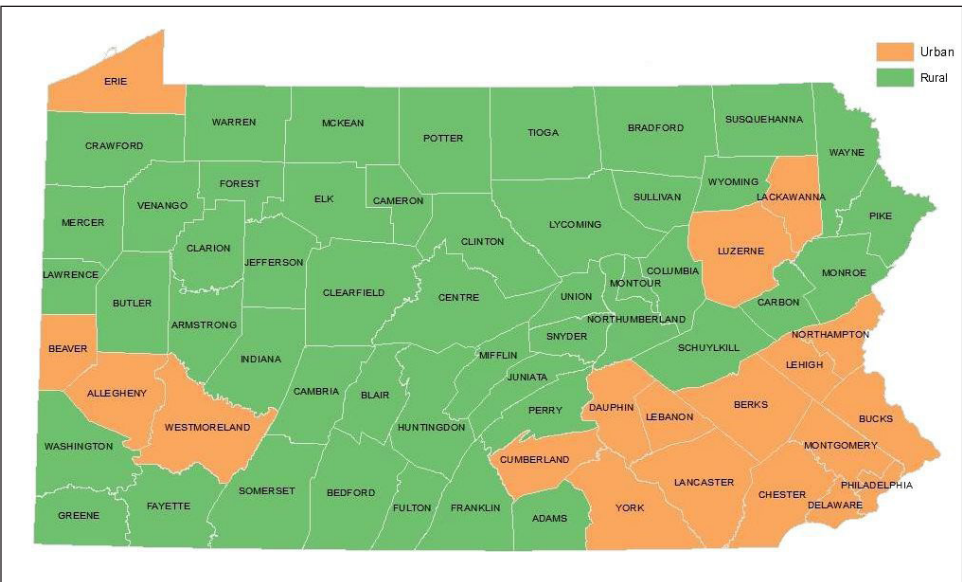


Figure 1. Rural and urban counties in Pennsylvania.

As ovarian cancer clinical trials are an important treatment option for cancer patients and critical to generating scientific evidence in a disease with significant burden and high unmet need, understanding trial accessibility to populations is essential to addressing current barriers to sufficient patient recruitment in trials. GIS analysis is used to examine areas that lack access to ovarian cancer clinical trials in Pennsylvania. ArcGIS 10.6 and 10.7 were used to conduct the analysis. Two GIS methods were used: suitability analysis and a Huff gravity model.

Suitability analysis

In order to examine a state-wide perspective, a suitability analysis was conducted. Suitability analysis in GIS examines an area for suitability for a particular usage. Suitability analysis has been widely used to examine areas suitable for particular land uses, such as housing development. However, suitability analysis has many applications and has been used to examine access to health care and other services (Mishra et al. 2019; Case and Hawthorne 2013). In a suitability analysis, multiple variables are considered in order to find locations that are most suitable for a particular variable. The variables are ranked from low to high and these are combined to determine an overall suitability.

In this project we examine suitable locations for ovarian cancer clinical trials, or in other words, places that demonstrate vulnerability to ovarian cancer. Lack of access to ovarian cancer trials means a limited access to trials as

a treatment option. In order to identify areas in Pennsylvania that lack such access, a suitability analysis was conducted at the county level. This analysis identifies areas that have risk factors for ovarian cancer as outlined above in the literature: number of ovarian cases per 2015 female population, existing number of ovarian cancer clinic trials, poverty status, and non-white populations. This analysis returns results at the county level by determining counties that show more vulnerability for women with ovarian cancer in terms of likely access to trials. Because clinical trial sites are often chosen for the presence of primary investigators who are specialist or sub-specialist experts in a particular disease, the presence of a clinical trial could also be considered a proxy measure for access to treatment centers with a high level of expertise in a particular disease.

The county level suitability analysis was conducted with readily-available data available from the Pennsylvania Department of Health and the US Census Bureau. Through the Pennsylvania Department of Health Enterprise Data Dissemination Informatics Exchange (EDDIE), information was obtained about incidents of ovarian cancer cases from 2011-2015. Due to the status of ovarian cancer as a relatively rare disease, with annual incidence in the United States thought to be approximately 11.0 per 100,000 women, sample sizes on a year to year basis are small when analyzed at the state and county level.

Ovarian clinical trial locations were obtained through the NIH Clini-

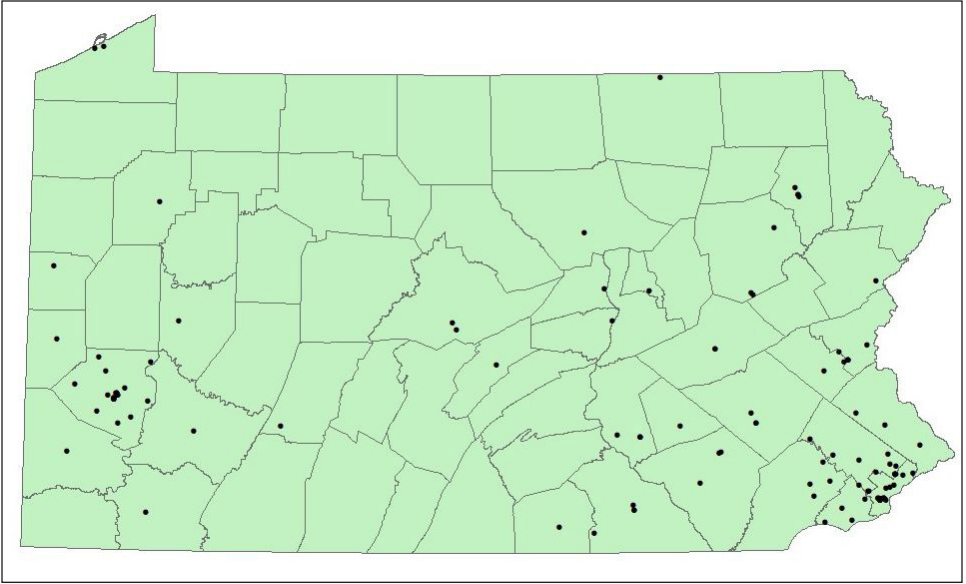


Figure 2. *Ovarian cancer clinical trial locations.*

calTrials.gov and geocoded (Figure 2). (Several trials did not give specific addresses and they were excluded from the study, while several trials had the same address and they were geocoded separately.) Socioeconomic data was obtained from the US Census Bureau 2015 American Community Survey 5-year data for poverty status and race.

Maps were created for each of the four variables: cases per 2015 female population, number of trials in each county, percent of population in poverty, percent of the population that is non-white. In each map the variable was classified into five equal interval categories, with some manual adjustment necessary. With three of the variables—cases, poverty and race—the rank increases with an increase in the variable. For example, the more cases of ovarian cancer, the higher the vulnerability. The number of trials variable

rank decreased with increased number, as the more trials that exist in an area, the better access to treatment. Each map was then converted to raster and the counties were ranked from 1-5 for each variable. They were combined using the Weighted Sum tool to create an overall ranking of vulnerability.

Gravity model

While understanding difference at the county level is essential to determine areas state-wide that lack access to ovarian cancer treatment, we hypothesized that differences in likely level of access would also exist within counties. Some counties in Pennsylvania are large, and the presence of a single clinical trial does not guarantee easy access to patients within county borders. In addition, some counties may have no clinical trials, but may be in close proximity to trials in a neighboring county.

To further understand accessibility from a more local perspective, a gravity model of spatial interaction was conducted. The Huff gravity model finds the likelihood of interaction between origins and locations based on distance, the origins being census tracts centroids and locations being the ovarian cancer trials. A Huff model extension for ArcMap was obtained (Huff Model 2013). Pennsylvania census tracts were obtained from the US Census Bureau. In the Huff model origins can be ranked on their level of attractiveness, but in this model all trials are ranked as similar attractiveness. The following is the basic Huff gravity model equation used (Huff 2003):

$$P_u = \frac{A_j \frac{1}{d_{ij}}}{\sum_x A_x \frac{1}{d_{ix}}}$$

P = the probability for interaction from census tracts to ovarian cancer trials; A = the attractiveness of the trial location (this was

left equal for all trials); d = distance from the centroid of the census tract to the trials

The maximum value from each census tract was extracted to determine the highest likelihood for interaction to an ovarian cancer trial.

Expected findings

(1) We expect to find more vulnerability to ovarian cancer in rural counties of Pennsylvania, and more ease of accessibility in urban counties. (2) We expect to see difference of accessibility within counties. Census tracts within counties will vary their accessibility to ovarian cancer trials.

Results and Discussion

The results are shown below of the suitability analysis and the Huff gravity model analysis. Figure 2 shows the geocoded ovarian cancer clinical trial locations.

Figure 3 demonstrates that overall, the number of cases per 2015 population



Figure 3. Percentage of ovarian cancer cases per 2015 population

is low throughout the state. Even though ovarian cancer affects a small percent of the female population, geographic difference is evident. The percentage of the 2015 female population with ovarian cancer ranges from 0.0411489% to 0.130548%. Table 1 ranks the counties from low to high in their rate of incidence. The highest five ranking counties Clearfield, Susquehanna, Clarion, Somerset, and Sullivan are all rural counties and they have between a 297% to a 319% higher percentage of occurrence than the lowest incidence Fulton County. As Figure 3 shows, areas with the highest rankings in the 4 or 5 categories are found throughout the state, however, most are in the rural areas.

The higher number of trials (and lower rankings) are found particularly in the urban counties of Philadelphia and Allegheny (Figure 4). Smaller number of trials are found in some urban and rural counties. Many counties have

no trials, which have the highest ranking.

Pennsylvania demonstrated geographic difference within the variable of poverty (Figure 5). Philadelphia County has the highest percentage of poverty by far compared to other counties. Counties in the second highest ranking, level 4, tend to be more rural. The least amount of poverty is shown in counties near Philadelphia and Pittsburgh, as well as centrally located counties.

Counties with the highest percentage of non-white residents include Philadelphia, as well as several other urban and rural counties (Figure 6). The lowest percentage of non-white residents is found in much of the northern and central parts of the state with the exception of Centre County.

The four variables above were combined using the Weighted Sum tool to determine an overall vulnerability for ovarian cancer, and they were each



Figure 4. Ovarian cancer trial rank. Higher numbers of trials are represented by a low value, representing lower vulnerability to cancer.

Table 1. Cases per 2015 female population (from low to high).

County	% of Cases		County	% of Cases
FULTON	0.04116		CAMBRIA	0.07786
SNYDER	0.04946		LANCASTER	0.07829
ARMSTRONG	0.05557		LEBANON	0.07926
ELK	0.05692		CARBON	0.07933
INDIANA	0.05728		MONROE	0.07993
PHILADELPHIA	0.05813		MERCER	0.08022
SCHUYLKILL	0.05846		CAMERON	0.08187
BERKS	0.06075		WAYNE	0.08257
PIKE	0.06342		MONTOUR	0.08373
CENTRE	0.0638		ERIE	0.08383
CLINTON	0.0639		MIFFLIN	0.08437
GREENE	0.06562		BUTLER	0.08505
COLUMBIA	0.06622		CHESTER	0.08606
DAUPHIN	0.06788		LUZERNE	0.08671
BLAIR	0.06792		BUCKS	0.08765
NORTHUMBERLAND	0.06885		WARREN	0.08797
VENANGO	0.06929		BEAVER	0.08909
UNION	0.0693		LAWRENCE	0.09107
LEHIGH	0.06937		MONTGOMERY	0.09113
CRAWFORD	0.06942		LACKAWANNA	0.09148
PERRY	0.0705		POTTER	0.09216
FRANKLIN	0.07086		WESTMORELAND	0.0935
YORK	0.07106		MCKEAN	0.0959
WYOMING	0.07136		NORTHAMPTON	0.09617
ADAMS	0.0719		JUNIATA	0.09642
BEDFORD	0.07322		FOREST	0.09852
HUNTINGDON	0.074		FAYETTE	0.09924
LYCOMING	0.07412		BRADFORD	0.10139
WASHINGTON	0.07419		TIOGA	0.10334
JEFFERSON	0.0755		CLEARFIELD	0.1205
CUMBERLAND	0.07683		SUSQUEHANNA	0.1235
DELAWARE	0.07701		CLARION	0.12353
ALLEGHENY	0.07767		SOMERSET	0.1273
			SULLIVAN	0.13055

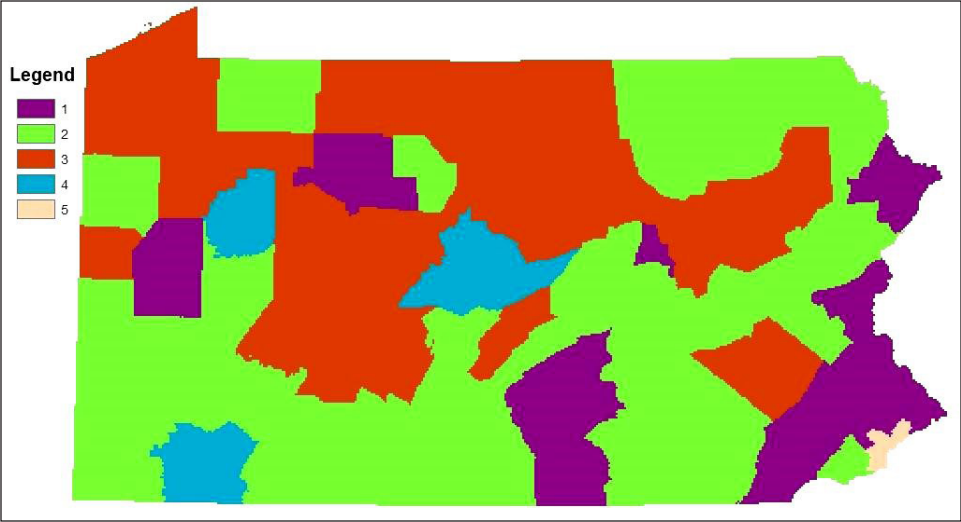


Figure 5. Poverty rank by county in Pennsylvania.

weighted equally. Geographic difference is revealed in the overall vulnerability ranking. The map shows that the major urban metropolitan areas of Philadelphia and Pittsburgh have low to moderate rankings, with the exception of Delaware County (Figure 7). Many of the counties that demonstrate the high-

est vulnerability are rural.

The vulnerability rankings were divided into five equal interval categories and the results are shown in Table 2. Of Pennsylvania's 67 counties, 19 (or 28%) are urban and 48 (or 72%) are rural. The two categories demonstrating the highest level of vulnerability to

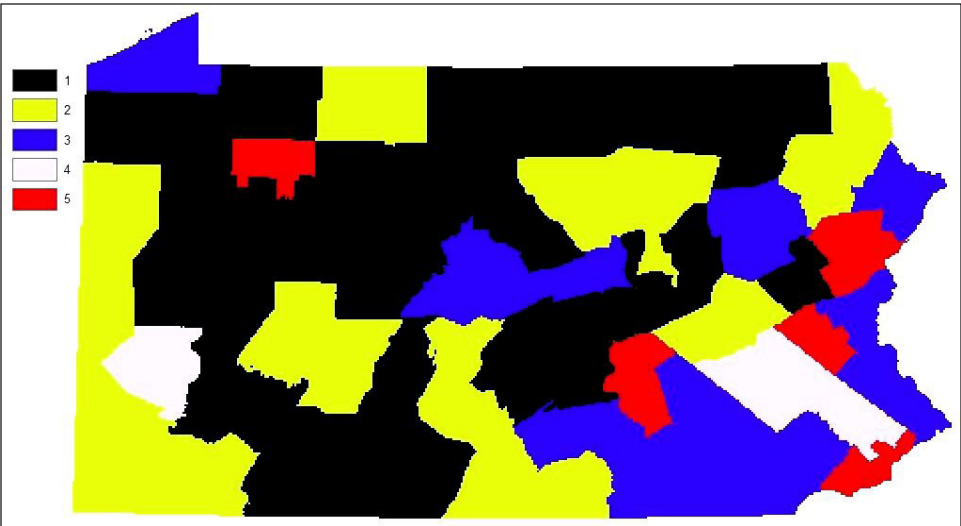


Figure 6. Rank of percent non-white.

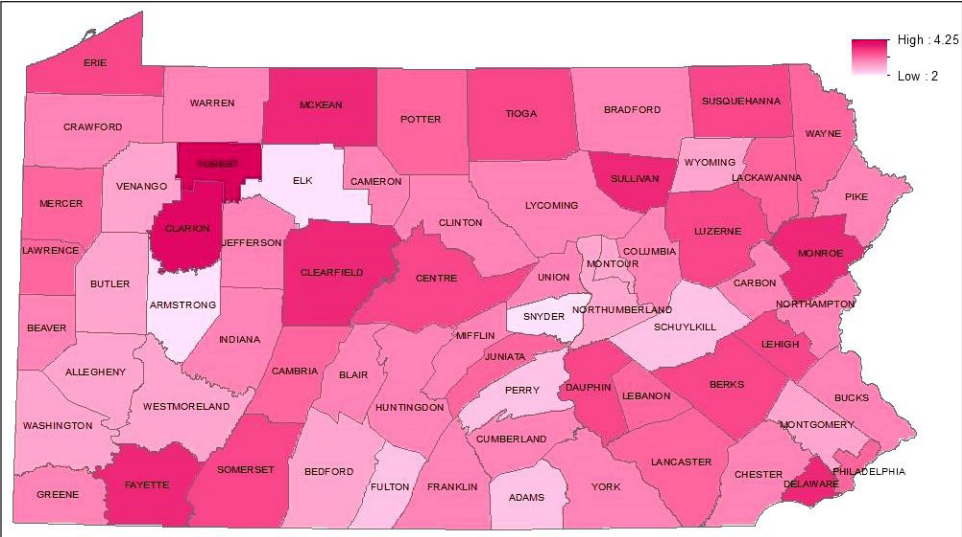


Figure 7. Vulnerability to ovarian cancer.

ovarian cancer, which are labeled high, are 100% and 86% rural. This reveals, as expected, that counties lacking access to ovarian cancer trials are mainly rural. However, the lowest category includes one county that is rural, and the second lowest category is 73% rural, which is very close to the percent of counties in Pennsylvania that are rural, 72%. Many urban counties appear in the middle ranking category.

Gravity model

Using the methods described above, the probability for interaction from each Pennsylvania census tract to ovarian cancer clinical trials were determined. The results (Figure 8) show the highest probability each census tract returns to a trial.

The gravity model results demonstrate that difference in accessibility exists within counties. There are larger counties that have low accessibility with

Table 2. Vulnerability by interval categories.

Counties	Vulnerability	Urban	Rural	Total	% Urban	% Rural
High	3.8-4.25	0	1	1	0	100
High	3.35-3.8	1	6	7	14.2857	85.7143
Middle	2.9-3.35	9	10	19	47.3684	52.6316
Low	2.45-2.9	9	24	33	27.2727	72.7273
Low	2-2.45	0	7	7	0	100
Total		19	48	67	28.3582	71.6418

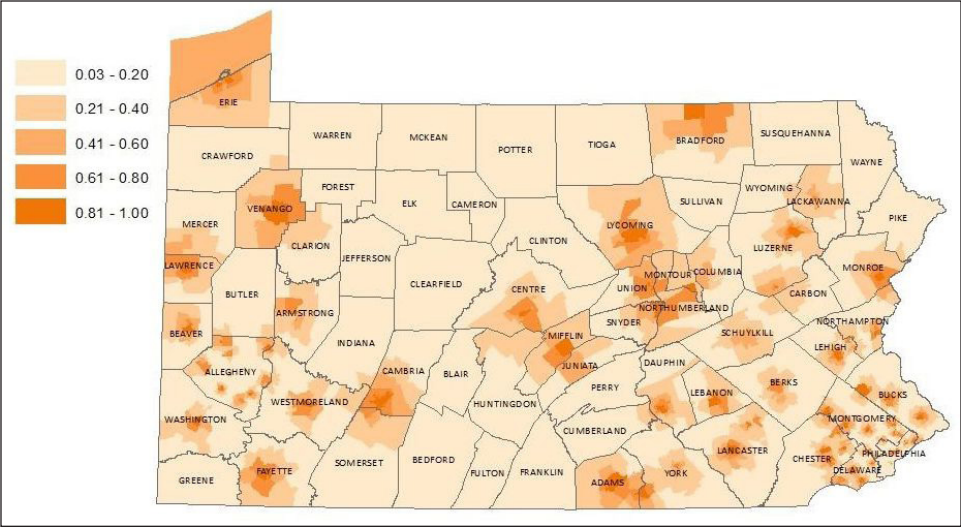


Figure 8. Huff probability for interaction with ovarian cancer trials by census tract.

increased distance from a trial. Other counties that have no clinical trial have some accessibility to trials in other counties, for example Huntingdon and Clarion counties. This demonstrates that accessibility to cancer clinical trials must be considered at both the county and local levels.

Limitations

Suitability Analysis: Some of the limitations to the analysis include the classification, the variables chosen, and the removal of clinical trials with no address. In order to create five categories for each of the four variables equal interval classification was used, but some manual adjustment was necessary. Choosing a difference classification could alter the results. The four variables chosen were those based on vulnerabilities to ovarian cancer identified through the literature, but other variables may be considered also.

Gravity Model: The attractiveness was left equal for each of the clinical trials. Future research could investigate factors such as availability for new patients in the trials, or number of patients accepted that may provide an attractiveness factor. The distance from the centroid of the census tract to the clinical trials was used to determine accessibility. While it was beyond the scope of this project to conduct a network analysis, future research could examine road networks to expand the understanding of accessibility.

Conclusion

This project aims to be a first step in understanding accessibility to ovarian cancer clinical trials in Pennsylvania and expanding the use of GIS to study public health issues. The results reveal that while counties throughout the state exhibit vulnerability, the number of rural counties that have rank in the “high”

categories for vulnerability to ovarian cancer is more than the Pennsylvania average of rural counties. The “low” ranking vulnerability categories include about an average number of rural counties, compared to the Pennsylvania average. The number of urban counties is disproportionately high in the “middle” ranking category. These counties often have some accessibility to ovarian cancer clinical trials, but also have higher than average percentage of non-white population and populations in poverty. More research is necessary at the local level to examine if traditionally disadvantaged populations are equally represented in the cancer trials; research from literature examining representation in trials at a national level would indicate that this is not likely to be the case. Planners, public health officials, and government officials can use this information to create policy to address this vulnerability. As ovarian cancer is a tumor type with high unmet need, a high risk of death for all individuals diagnosed, and a death risk for African American women disproportionate to the incidence of diagnosis in this population, it is a target area for clinical research and drug development. However, clinical trials can only be successful when they adequately accrue patients, and trial results are only able to be extrapolated to real-world populations if the trial population is representative.

While the use of GIS to examine public health issues has greatly expanded in recent years, there is significant potential to increase the use of this method in the field of public health. This project

aims to be a starting point to examining geographic accessibility to cancer trials. Future research can expand on these results to understand further issues such as how people get to cancer trials, the possibility of acceptance in a nearby trial, what populations are currently in the trials, and what public policies are necessary to expand the accessibility. This model can be adapted for other types of cancer and locations.

Acknowledgement

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