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A systematic review of instrumental variable analyses using geographic region as an instrument

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ABSTRACT

Background: Instrumental variables analysis is a methodology to mitigate the effects of measured and unmeasured confounding in observational studies of treatment effects. Geographic area is increasingly used as an instrument.

Methods: We conducted a literature review to determine the properties of geographic area in studies of cancer treatments. We identified cancer studies performed in the United States which incorporated instrumental variable analysis with area-wide treatment rate within a geographic region as the instrument. We assessed the degree of treatment variability between geographic regions, assessed balance of measured confounders afforded by geographic area and compared the results of instrumental variable analysis to those of multivariable methods.

Results: Geographic region as an instrument was relatively common, with 22 eligible studies identified, many of which were published in high-impact journals. Treatment rates did not vary greatly by geographic region. Covariates were not balanced by the instrument in the majority of studies. Eight out of eleven studies found statistically significant effects of treatment on multivariable analysis but not for instrumental variables, with the central estimates of the instrumental variables analysis generally being closer to the null.

Conclusions: We recommend caution and an investigation of IV assumptions when considering the use of geographic region as an instrument in observational studies of cancer treatments. The value of geographic region as an instrument should be critically evaluated in other areas of medicine.

1. Introduction

The randomized controlled trial is considered the gold standard for determining comparative treatment effectiveness. However, many treatment comparisons of interest have not been subject to randomized trials, at least in some cases because a trial would be of low feasibility due to expense, or because of low patient tolerance for random assignment. Observational data are often used in place of randomized trials to make inferences about treatment effectiveness, but are prey to confounding bias due to patient selection. There are several statistical methods available to control for measured confounding in observational studies, including multivariable regression and propensity score approaches.

Instrumental variable (IV) methods are an alternative approach that were originally developed by economists and more recently applied for causal inference in healthcare research [1]. The purported advantage of instrumental variable methods over multivariable models or propensity scores is that they balance both observed and unobserved confounders. The method involves identifying an instrument, a variable that is associated with treatment but does not influence outcome, other than through the mechanism of treatment. Randomization is typically an excellent instrument as there is generally a high level of agreement between randomized treatment assignment and treatment received but randomization itself has no direct effect on outcome; observational instrumental variables studies attempt to identify instruments with similar properties to randomization. A classic example of a healthcare instrument is distance from a healthcare facility providing a particular type of intervention. Distance will be a valid instrument where, as is often the case, it affects the likelihood of receiving the intervention but not outcome other than through the effect of treatment on outcome. For instance, a woman living a long way from a mammography facility may be unwilling to travel for a mammogram, but is not otherwise at

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Abbreviations: IV, instrumental variables; HRR, hospital referral region; HSA, healthcare service area; RR, relative risk; CI, confidence interval; HR, hazard ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; AJCC, American Joint Committee on Cancer; SEER, surveillance, epidemiology, and end results; SES, socioeconomic status; CCI, charlson comorbidity index

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increased risk of breast cancer death. Ideally, a good instrument satisfies three assumptions: the IV predicts treatment, there is no direct effect of the instrument on outcome except through treatment, and no unmeasured confounding between instrument and outcome [1].

Geographic area has recently been used as an instrument in studies of cancer treatments [2,3]. Through the Dartmouth Atlas program, patterns of use of hospital care known as hospital referral regions (HRR) or healthcare service areas (HSA/HCSA) were established. HSAs are defined by assigning ZIP codes to the hospital area where the greatest proportion of their Medicare residents were hospitalized. HRRs were defined by assigning HSAs to the region where the greatest proportion of major cardiovascular procedures were performed, with minor modifications to achieve geographic contiguity, a minimum population size of 120,000, and a high localization index [4]. Where geographic region is used as the instrument, treatment prevalence within HSAs or HRRs are calculated and used in the estimation of treatment effect [5].

As is well known from the work of the Dartmouth atlas, there are important variations in treatment rates across geographic regions. However, extreme variation across geographic regions would be unexpected. For instance, for the purposes of ensuring that we provide high quality care, it is important to bring to light if 50% of patients in some areas receive a particular treatment compared to 30% of patients in other areas, as this suggests over or undertreatment in at least one of the two areas. But we would be surprised if, say, treatment rates were 80% in one region versus 20% in another.

We hypothesized that geographic region is not strongly associated with cancer treatments and that patient characteristics vary regionally, both of which would suggest that geographic region is not a good instrument. To investigate these hypotheses, we performed a systematic review of studies where geographic region was used as an instrument in an observational study of a cancer treatment. Our aims were to determine the prevalence of this type of analysis, assess the association between treatment and geographic region, document the degree to which geographic instruments balance measured confounders and compare inferences from instrumental variables analyses with traditional multivariable approaches to observational data.

2. Methods

Using PubMed and Google Scholar, we searched for cancer studies, defined as those that examined the effect of at least one treatment, intervention, or screening in cancer patients. The terms “instrumental variable” or “instrumental variables” and “cancer” were searched in conjunction with the following search terms to identify geographic instruments: “hospital service area”, “healthcare service area”, “HCSA”, “HSA”, “hospital referral region”, “HRR”, “geographic area”, and “geographic variation”. Eligible studies had to use instrumental variable analysis with area-wide treatment rate within a geographic region as the instrument, and were limited to those cancer studies using data from the United States. Data collected from these studies included general data on the research question being investigated: indication for treatment or type of cancer; treatment(s) or intervention(s); sample size; definition of geographic area used; geographic area-based instrumental variable; and range of treatment rates between geographic areas. We also collected information on methodology and the types of analyses performed: types of statistical methodology used for instrumental variable and non-instrumental variable analyses; the F-statistic from the test of the association between treatment rate and instrument; outcome(s) of interest; central estimates of effect size with 95% confidence interval for instrumental variable analysis and any other analyses reported, such as propensity score or multivariable analyses; any covariates that remained unbalanced in the instrumental variable analysis.

In many studies, results were presented for more than one outcome, more than one type of statistical methodology, or more than one subset of the cohort. For studies that presented results for multiple outcomes, we chose the outcome for which comparable results on the same scale were available for both instrumental variable and non-instrumental variable analyses. If there was more than one outcome with comparable results, the outcome chosen as primary by the author was selected. If no primary outcome was specified, overall survival was used. If an outcome was assessed at multiple time points, the earliest time point was chosen, as in all studies outcomes at multiple time points were assessed independently, rather than by using longitudinal methods.

For studies which reported multiple IV methodologies we gave preference to the two-stage residual inclusion methodology as 2SRI has been found to provide a less biased result [6,7]; in cases where this was not available we used two-stage least squares methodology. If neither of the two-stage common methodologies was used, we reported the single IV methodology given by the author. In one case IV results were presented using both a binary and categorical categorization of the IV [8]. We reported only the results based on the binary-defined instrument since binary categorization is reported more commonly than categorical subclassifications.

If a study provided more than one type of non-instrumental variable analysis, we chose the methodology that presented estimates of effect size that could be compared to the instrumental variable analysis. Given that standard multivariable models and propensity scores methods tended to give very similar results, we chose to report the multivariable analysis if more than one comparable analysis was performed. If no multivariable models were provided, propensity scores, of whatever form, were used. If a cohort was divided into two or more subsets, the subset with the larger sample size was chosen for the purpose of comparing results.

The reporting of covariate balance was based on specific references by the study authors in the text. If the authors did not mention covariate balance, it was based on *p*-values ($\alpha = 0.05$) presented in tables showing the balance of covariates across levels of the instrumental variable.

3. Results

The initial search resulted in 279 potentially eligible studies (Fig. 1). Of these studies, 245 were excluded on initial review. Full manuscripts were reviewed for 33 studies, with another 11 studies then excluded. This resulted in 22 eligible studies included in our systematic review. The most commonly studied cancers were prostate cancer, with ten studies, followed by lung and breast cancers. The specific reporting of how instrumental variable analysis was performed varied among the studies. Eleven provided a treatment effect estimate from the instrumental variable analysis and an estimate from a non-instrumental variable analysis that could be compared on the same scale. Fourteen studies reported information on the range of treatment rates seen in each geographic region.

Regardless of how the IV was included in the analyses, treatment rates were most commonly reported as either the mean rate for regions above and below the median value of the instrument or the prevalence in the lowest versus the highest quintile. However, there was considerable variation in reporting. For example, Posner et al. [9] report no summary of treatment rates, Kuo et al. [10] report an overall rate, Hadley et al. [11] and Wright et al. [12] report the average rate above and below the median, and McDowell et al. [13] report the average rate for the highest and lowest quintile. One study did not report treatment rates by low use and high use areas, but reported a range of treatment rates from 0% to 60% over 134 regions, with a median treatment rate of 12% [14]. Most studies report a narrow range of treatment rates, which indicates a weak association between geographic region and treatment. The smallest difference between high and low use areas was 4.8% [8], while the largest difference was 30.7% [15]. The majority of studies reported a difference in treatment rates between high and low use areas of 5% to 20% (9 of 14 studies).

Regardless of the difference in effect size between IV and non-IV analyses, eight out of eleven studies with comparable results rejected

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