Cancer Mortality and Research Outcomes in a Rural State

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ABSTRACT

Background: North Dakota is a rural state with high rates of cancer. Determining how various demographic, geographic, and funding factors contributed to cancer incidence on a state and county level helps improve cancer prevention and control.

Objectives: We examined cancer incidence rate trends by demographic (sex and ethnicity) and geographic (county, population, rural/frontier status) factors. We also examined cancer funding and research output by year.

Methods: Cancer incidence rates were obtained from the North Dakota Cancer Statewide Registry and stratified by sex, ethnicity, and county. US cancer rates also were obtained for comparison. Generalized linear models were used to compare overall incidence rates and yearly trends.

Results: Male melanoma incidence rates increased faster than the US average across year ($P = 0.020$). Incidence rates for prostate, lung, and colorectal cancer among American Indians/Alaska Natives (AI/AN) decreased faster than Whites across year ($P < 0.001$, $P = 0.001$, $P < 0.001$, respectively). Four counties—2 for breast cancer and 2 for prostate cancer—had differential trends compared to the North Dakota average across year ($P = 0.011$, $P = 0.029$; $P = 0.046$, $P = 0.042$). County-level lung cancer incidence rates were positively correlated with county population size, while rates for cervix/uteri were negatively correlated ($P = 0.001$, $P = 0.023$). Funding from the National Institutes of Health for North Dakota increased across year along with cancer papers published increased ($P < 0.001$, $P < 0.001$).

Conclusions: Examining state and county data revealed several surprising trends and the need for a more fine-scale approach to cancer cause, control, and prevention.

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INTRODUCTION

Cancer remains a difficult disease to treat and a major source of mortality despite a decades-long nationwide decrease in incidence.[1] Using a rural state as a natural laboratory, we examined incidence rates for top cancers by sex, ethnicity, county, and population size. We also examined funding level by year to understand resource impact.

North Dakota and Cancer

North Dakota is a rural state with a small population (760,777) and has been called a natural laboratory due to high cancer incidence rates and high county-level variation.[2] Demographically, Whites are the ethnic majority (85%), with American Indian/Alaskan Natives (5.4%) as the only other ethnic group with a population size big enough for analysis. Lung cancer incidence is declining,[3] although rates are higher for American Indian/Alaskan Natives (AI/AN) versus non-Hispanic Whites.[4] Both the incidence and mortality of liver cancer in North Dakota are the lowest in the nation.[5,6]

Unfortunately, some North Dakota cancer rates are elevated. Despite dropping for 3 decades, oral cancer in the state has risen in recent years.[7] Prostate cancer mortality is high compared to the national average,[8] as is thyroid cancer;[2] and colorectal cancer incidence in North Dakota is one of the highest in the nation.[9]

Sex and Ethnicity

Incidence and mortality across specific cancer types differ by sex and ethnicity, often significantly.[10] AI/ANs are an underserved population with higher rates of illness and mortality and lower access to health resources.[11] They are less likely than the general public to have preventive measures like screening for colorectal, prostate, and breast cancer.[12]

While total cancer incidence rates are lower in the AI/AN population than those for non-Hispanic Whites nationally, AI/ANs in the Northern Plains region (North Dakota, South Dakota, Nebraska, and Iowa) have higher cancer incidence rates[13] and the highest mortality rates of AI/ANs in any US region.[14] For specific cancer types, both male and female AI/ANs have notably higher colorectal cancer mortality rates.[15]

County and Rural Status

North Dakota has 53 counties and is the 19th-largest state with the 47th-highest population. The North Dakota Center for Rural Health classifies 6 counties as urban, 10 as semi-rural, and the majority—37—as rural. Rural populations are more vulnerable to health issues because of comorbidities such as cancer, heart disease, diabetes, hypertension, and obesity.[16,17] Rural areas also have older age structures.[18] These vulnerabilities, combined with reduced health care access, make rural areas potentially high areas of cancer incidence and mortality.[19]

Cancer Funding

Despite its high burden of cancer, North Dakota has low access to cancer research funding. Indeed, while the American Cancer Society currently supports 739 cancer research grants, North Dakota—along with Montana and South Dakota in the Great Plains Region—holds no current grants. Meanwhile, the North Dakota cancer care expenditure estimate for 2010 was $274.2 million, distributed among 8 cancer categories.[20] To address this issue, North Dakota became part of the Institutional Development Award (IDeA) Program, a National Institutes of Health (NIH) initiative to support states with low historical funding. In the last 4 reported years of NIH grants (2015-2018), North Dakota had 41 awards for general cancer. There were 5 grants towards 2 prostate projects, 4 grants for 2 colorectal projects, and 2 grants for 1 lung project. Since 1976, there have been 151 cancer-related journal articles reported by the 2 research universities—the University of North Dakota (UND) and North Dakota State University (NDSU).

Hypothesis

We hypothesized that incidence rates by sex and ethnicity would be significantly higher for prostate, colorectal, and thyroid cancers than the national average, but that all trends would be comparable. We also hypothesized that there would be county-level differences in cancer trends, rural counties would have higher cancer rates, and that cancer funding would be increasing by year to meet the demands of high cancer incidence rates.

METHODS

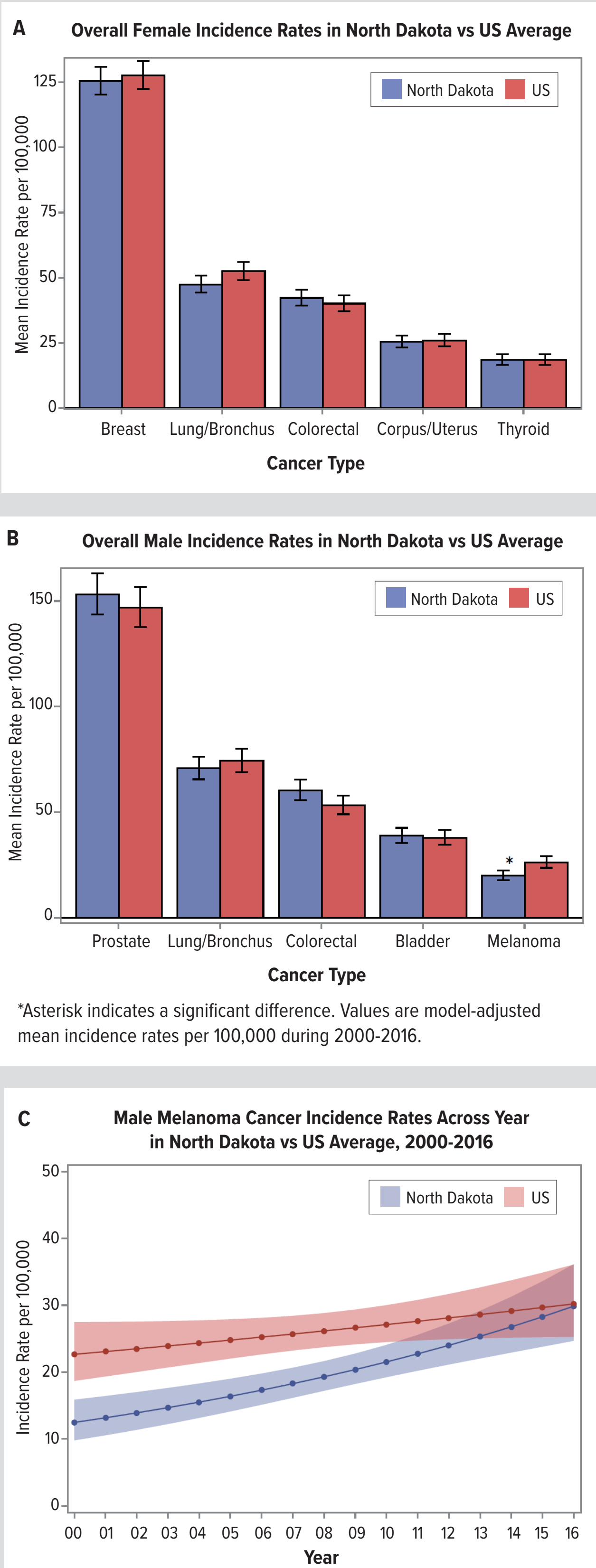
Data Collection

Cancer Rates: North Dakota cancer incidence rates, age-adjusted per 100,000, were obtained from the North Dakota Statewide Cancer Registry (ndcancer.org) by submitting a Type I data request. Institutional Review Board approval was not required because the data were deidentified and aggregated. Data were obtained for all available years (1997-2016) and included prostate, breast, lung, colorectal, bladder, melanoma of the skin, thyroid, and corpus/uterus cancers; non-Hodgkin's lymphoma; and leukemia. The top 5 cancers for males (prostate, lung, colorectal, bladder, melanoma) and females (breast, lung, colorectal, thyroid, corpus/uterus) were stratified by sex. Only incidence rates for colorectal, lung, prostate, and breast cancer had enough data to stratify by ethnicity (White, AI/AN). Overall county-level rates were available for most counties, but yearly rates were limited to all but a few counties, because counts lower than 10 in any category were unavailable as they were suppressed due to confidentiality policies. Similarly, county rates could not be separated by ethnic group or sex due to suppressed rates. To compare to the national average, US cancer incidence rates were obtained from 21 areas of the Surveillance, Epidemiology, and End Results (SEER) Program database.[21]

Geography: Each county was classified with a rural (rural, semi-urban, and urban) and frontier status (yes/no) using maps from the North Dakota Center for Rural Health (ruralhealth.und.edu). Urban counties were designated as having at least 1 city with a population of 50,000 or having close ties with an adjacent county with such a city. Semi-rural counties were designated as having at least 1 town or city with a population of 2,500 to 49,999, and rural counties as having no towns with a population greater than 2,500. Frontier counties were designated as having population densities of less than 7 persons per square mile. Population size by county was obtained from the US Census Bureau, based on 2010 estimates. They were natural log-transformed so that population size would approximate a Gaussian distribution clearer analysis and visualization.

Cancer Funding: Funding information was obtained from 3 sources: NIH Portfolio Online Reporting Tool (RePORT), the UND Grants Office, and the North Dakota Office of Management and Budget. All 3 were searched for cancer-based projects for the available year ranges of 1985-2020, 1994-2020, and 2010-2019; and the resulting numbers of projects and funding amounts were aggregated by year for the same range as the cancer incidence rates (1997-2016). Finally, Scopus was searched by institution for each of North Dakota's 2 research universities (UND and NDSU) for 1997-2016 using the keyword "cancer." The number of cancer-related journal articles was aggregated by year.

Figure 1. Cancer Incidence Rates by Sex



*Asterisk indicates a significant difference. Values are model-adjusted mean incidence rates per 100,000 during 2000-2016.

Lines were generated from prediction mean values from a generalized linear model with a negative binomial distribution and bands are 95% confidence limits of the mean.

Statistical Analysis

Cancer incidence rates can be modeled as a count variable with a Poisson distribution.[22] However, because the Poisson distribution is a special case of the negative binomial distribution and tends to have a better fit statistic (chi-square/degrees of freedom [df]), all models used in this analysis utilized a negative binomial distribution unless optimization could not be completed. *F*- and *t* statistics were calculated using SAS Studio Software, V.3.8 (2018; Cary, North Carolina).

Sex: Cancer incidence rates by year and sex from both North Dakota and the US average were considered together. Region was designated as either North Dakota or US. Male and female cancer incidence rates were modeled as a function of cancer type, region, and their interaction with a generalized linear model. Then, the incidence rates for each sex's top 5 cancers were modeled as a function of the interaction between year and region. Male bladder cancer incidence rates were modeled using the Poisson distribution, as optimization could not be completed with a negative binomial distribution.

Ethnicity: Cancer incidence rates by year were compared across the 2 major ethnic groups in North Dakota—Whites and AI/ANs. Cancer incidence rates were modeled as a function of ethnicity, cancer type, and their interaction. Then, for each cancer type that had enough data points (prostate, breast, lung, colorectal), incidence rates were modeled as a function of the interaction between year and ethnicity.

Geography: To compare county-level cancer incidence rates by year to overall North Dakota incidence rates, counties were first checked to determine if they had enough data points. Only counties that were missing 3 or fewer years (out of 20) were included. Counties that met the criteria were used in subsequent modeling. For each county and cancer type, the incidence rate was modeled as a function of the interaction between year and region, with the region as either the specific county or the state average.

Next, all cancers that had enough data points per year (lung, colorectal, kidney, prostate, breast, bladder, melanoma, thyroid, corpus/uterus, non-Hodgkin's lymphoma, and leukemia) were modeled by county as a function of the natural log of county population size. Then, cancer rates were modeled as a function of rural status (urban, semi-urban, rural) and a function of frontier status (yes/no). Because there were no urban counties that were also frontier counties, rurality and frontier status were modeled separately.

Funding: The number of cancer-related journal articles published by North Dakota institutions was modeled as a function of year. So was the number of NIH cancer grants, funding from NIH cancer grants, number of UND grants, funding from UND grants, and funding from the North Dakota state government.

RESULTS

Sex

Female incidence rates were not significantly different by region and cancer type (Figure 1A). In contrast, males had a significant difference ($F = 4.47$, $P = 0.002$). Model-adjusted melanoma incidence rates were significantly lower in North Dakota (20.0) compared to the US average (26.3) (Figure 1B). The yearly incidence trends for the top 5 female cancers in North Dakota were not significantly different than the US average. The same was true for yearly trends in all male cancers except melanoma ($F = 6.1$, $P = 0.020$). North Dakota melanoma rates rose faster than the US average in the last 2 decades (Figure 1C).

Ethnicity

There was no difference between overall cancer rates between Whites and AI/ANs when considering ethnicity alone. In the interaction model, both ethnicity ($F = 17.9$, $P < 0.001$) and the interaction between ethnicity and cancer type ($F = 5.8$, $P < 0.001$) were significant. AI/ANs had higher overall mean incidence rates (108.5 vs 86.8). AI/ANs had higher rates than Whites for colorectal (66.9 vs 51.2) and lung (114.8 vs 55.8) cancer, though only lung cancer incidence was significant (Figure 2).

The yearly incidence trends between Whites and AI/ANs were significantly different for prostate ($F = 22.1$, $P < 0.001$), lung ($F = 12.5$, $P = 0.001$), and colorectal ($F = 41.2$, $P < 0.001$), but not breast cancer. AI/AN prostate cancer incidence rates decreased faster by year than Whites. White lung and colorectal cancer incidence rates were stable, while AI/AN rates decreased by year. By 2016, all 3 AI/AN cancer rates were comparable to Whites.

Geography

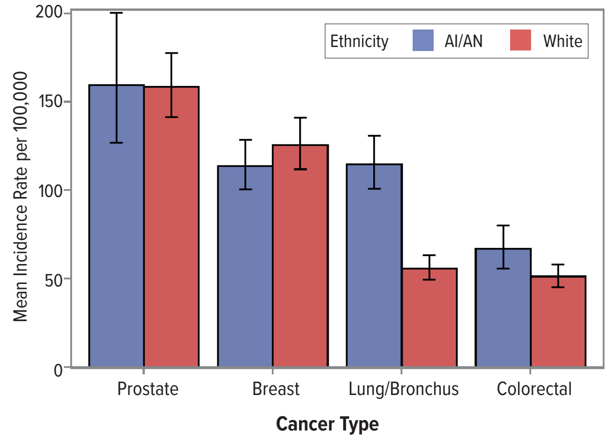
A limited number of counties had enough data points to analyze (prostate, n = 9 counties; breast, n = 8 counties; lung, n = 7 counties; colorectal, n = 6 counties; bladder, n = 3 counties; uteri, n = 1 county). Of those, 4 counties had significantly different cancer incidence trends across year compared to North Dakota overall. Two counties had breast cancer incidence rates that significantly fell while the overall state rate remained stable ($F = 7.2$, $P = 0.011$; $F = 5.2$, $P = 0.029$). Two other counties had prostate cancer incidence rates that did not decrease as fast as the state rate ($F = 4.3$, $P = 0.046$; $F = 4.4$, $P = 0.042$).

Only lung and corpus/uteri cancer rates were significant across population size. Lung cancer incidence rates significantly increased ($t = 11.7$, $P = 0.001$) with log population size, while corpus/uteri cancer rates decreased significantly ($t = 5.6$, $P = 0.023$) (Figure 3). Across rurality status and frontier status, only lung cancer by frontier status was significant ($t = 16.8$, $P < 0.001$). Model-adjusted lung cancer incidence rates were higher in nonfrontier counties (60.7) than frontier (49.7).

Funding

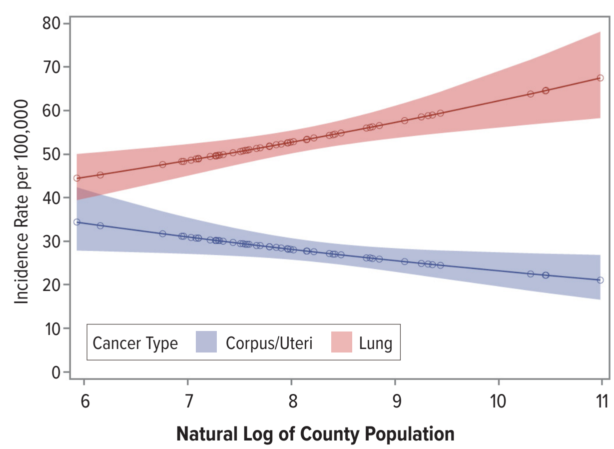
The number of cancer-related journal articles, NIH grants, and NIH funding increased significantly by year ($t = 363.4$, $P < 0.001$; $t = 16.3$, $P < 0.001$; $t = 35.6$, $P < 0.001$, respectively) (Table). Neither UND grants nor UND funding were significant by year, and data were insufficient to model government funding.

Figure 2. Cancer Incidence Rates by Ethnicity, 2000-2016



Overall incidence rates for American Indians/Alaska Natives (AI/AN) compared to Whites. Values are model-adjusted mean incidence rates per 100,000.

Figure 3. Cancer Incidence Rates by Population



Overall county lung and corpus/uteri cancer incidence rates by log county population. Lines were generated from prediction mean values from a generalized linear model with a negative binomial distribution; bands are 95% confidence limits of the mean.

DISCUSSION

Sex

Male melanoma was lower in North Dakota compared to the US average when averaged across all years. A recent study on ultraviolet-attributed melanoma rates backs this assertion; North Dakota was ranked the 41st highest.[23] The point of interest is

Table. Number of Cancer Paper Publications and NIH Grants and Information on NIH Funding for the University of North Dakota and North Dakota State University, by Year

Year	Published Cancer Papers	No. of NIH Grants	Funding From NIH Grants (Millions)
1997	25	2	0.34
1998	31	2	0.39
1999	29	4	0.74
2000	22	2	0.49
2001	21	2	0.66
2002	39	2	0.84
2003	49	2	0.64
2004	42	4	0.53
2005	54	3	0.84
2006	59	5	1.49
2007	59	14	3.41
2008	61	19	4.52
2009	69	18	4.88
2010	93	15	4.16
2011	103	11	2.59
2012	120	6	2.48
2013	143	5	4.15
2014	129	8	7.77
2015	146	10	8.36
2016	143	18	12.57

Abbreviation: NIH, National Institutes of Health.

that looking at the yearly trend, rates in the state are increasing faster. This was unexpected because the major risk factor for melanoma is ultraviolet (UV) light exposure. North Dakota has a low UV light climate and outdoor recreation does not appear to be a significant risk factor. The latest report from the Bureau of Economic Analysis showed that North Dakota had 2.2% of its gross domestic product from outdoor recreation compared to the 2.1% national average.[24] Regarding artificial UV sources, because North Dakota has not pursued data collection on tanning prevalence from national surveys, artificial UV exposure is unlikely to be a major risk factor.

However, it may be that North Dakotans have more acute sun exposures. In the 2012 Behavioral Risk Factors Surveillance System, compared to the nation overall, North Dakotans had a higher rate of sunburns (32.3% with at least 1 sunburn in the last year) compared to the overall US (21.28% unweighted, 26.36% weighted). North Dakota males had higher rates (33.9%) than females (30.8%).[25]

Ethnicity

As shown in other studies, AI/ANs have higher cancer incidence rates for overall cancers and lung/colorectal cancers separately. Our results agree with the most recent data from the North American Association of Central Cancer Registries,[26] as well as from research in the broader Northern Plains region.[4,27] The good news is that AI/AN cancer rates are falling significantly faster for prostate, lung, and colorectal cancers in North Dakota, and currently are on par with Whites' rates. This may be due to an increased focus on AI/AN communities. The most recent North Dakota Cancer Control Plan includes objectives to decrease smoking in American Indian adults as well as utilizing and evaluating cancer health disparity data.[28] Similarly, the North Dakota Colorectal Cancer Roundtable has a goal for an 80% colorectal cancer screening rate in every community and specifically recognizes the need to address disparities for American Indians. Furthermore, data from the Behavioral Risk Factors Surveillance System indicates that smoking rates in AI/ANs, while still elevated, are falling faster than non-AI/ANs. The percentage of AI/ANs who reported smoking every day was 48.5% in 2003 and dropped to 26.3% in 2019 (compared to 15% and 11.6%, respectively, in non-AI/ANs).

Geography

Most counties had the same yearly incidence trends for major cancers as North Dakota overall. However, 2 counties had falling breast cancer incidence rates compared to the level rate of North Dakota overall, and 2 counties had prostate cancer incidence rates that were not falling as fast as the state overall. This shows that cancer incidence rates are not uniform across even states, so county-level information can reveal more nuanced patterns.

It was interesting that lung cancer incidence increased by log population size while cervix/uteri decreased. Higher smoking rates—a risk factor for lung cancer—is typically higher in the US for rural areas (28.5%) than urban areas (25.1%).[29] Another risk factor, radon levels, does not vary by population size because all counties in North Dakota have zone 1 levels (>4.0 pCi/L). Therefore, it remains unclear why the state's lung cancer rates by population size are the inverse of what risk factors would predict. The dominant cause of cervical cancer is human papillomavirus (HPV), so women living in more urban areas conceivably have more access and education on HPV vaccination. This is supported by Centers for Disease Control and Prevention reports that found a 15-percentage point deficit of HPV vaccinations in rural versus urban areas[30] and lower rates of at least 1 HPV dose in nonmetropolitan areas (64.2%; 95% CI, 61.2-67.2) versus metropolitan areas (71.2%; 95% CI, 69.2-73.1).[31]

Another possible county-level difference in cancer incidence rates is the area deprivation index, which ranks socioeconomic status disadvantage. Counties with higher average indices could plausibly have higher incidence because of lack of access to health care services or lower rates of healthy behaviors. Using averaged state index values from the Neighborhood Index for North Dakota,[32] we explored the relationship between the indices and the incidence rates for lung, prostate, breast, and colorectal cancer. Only breast cancer had a significant relationship, and it was negative ($t = -2.02$, $P = 0.486$), meaning that counties with higher indices (more disadvantaged) had lower incidence rates of breast cancer. It seems that disadvantage status does not predict a higher cancer incidence, at least with univariate analysis.

Funding

Both extramural cancer funding (from NIH) and cancer output in the form of journal articles in North Dakota have increased over the past 2 decades. These trends are not just a reflection of the overall increase in NIH budget, which almost tripled from 1997 ($12.11 billion) to 2016 ($32.26 billion). North Dakota's funding increased during that timeframe an order of magnitude more–$342,596 to $12.57 million. Intramural funding does not appear to be increasing. However, UND's funding in 2018-2019 was double the next highest year, so could be increasing in the short term. Also, the shift from individual funding (research, prevention/control) to infrastructure-based funding (cancer registry, translational cancer collaborations) seems to provide a more permanent investment in cancer. Finally, there was only a decade's worth of data from the North Dakota government checkbook, so it is too soon to determine a trend. There may be changes in the fiscal year that are not appropriately reflecting the true trends.

Limitations

There were some limitations to this study. First, not all years (1997-2016) had reportable cancer incidence rates for AI/ANs. Out of the 20 years covered for breast, lung, colorectal, and prostate cancer, there were 18, 16, 9, and 5 years, respectively, reportable for each. This suggests, for colorectal and prostate cancer rates especially, that the true cancer trend may be significantly different from what could be calculated here. Second, most counties did not have enough cases (10 or more) to analyze. The ones that did have enough cases had higher populations, biasing the presentable analyses towards more populated counties.

CONCLUSIONS

North Dakota has surprising cancer incidence nuances. Despite being a state with low UV exposure, male melanoma rates are increasing faster than the national average. Cancer incidence rates for highly prevalent cancers are dropping among AI/ANs faster than Whites. Some counties have yearly incidence trends for breast or prostate cancer that deviate from the state average. Lung cancer incidence rates, despite possible risk factors that point towards an opposite trend, were more elevated in urban areas.

Future work on male melanoma trends in North Dakota would benefit from an individual-level analysis, possibly with a follow-up questionnaire with survivors on sun exposure and tanning usage. Similarly, an individual-level approach would provide a complete dataset by year for AI/AN cancer rates to confirm the decrease in the state-level lung, prostate, and colorectal cancer incidence and tease out possible underlying factors behind the decrease. Once the factors behind the declining incidence rates are understood, they could be applied to AI/AN communities in other regions. Finally, work remains to link cancer incidence with outcomes. One way would be to compare state-level cancer control plans and determine how objectives are met over time.

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