

NC Thyroid Cancer Panel Report and Recommendations

July 8, 2019

In spring 2019, an expert panel of epidemiologists, clinicians, and environmental scientists was assembled by the UNC Lineberger Comprehensive Cancer Center to identify research needs related to thyroid cancer incidence in North Carolina (NC). The panel was charged with developing recommendations for research to provide evidence that might help explain the elevated rates of thyroid cancer in several NC counties. The panel also was charged with recommending potential additional environmental, clinical, biologic, and epidemiologic monitoring of thyroid cancer in NC, and any other prospective resources to provide a basis for future investigations.

In developing its recommendations, the panel reviewed the NC Department of Health and Human Services (NC DHHS) Report on Thyroid Cancer in Iredell County (1), other data reports from the NC Central Cancer Registry, relevant NC DHHS reports, selected published reports on the epidemiology, biology, clinical aspects of thyroid cancer, and other scientific publications. In addition, input from a community meeting held on May 9, 2019 and an online public comment portal also were considered.

The meeting was jointly sponsored by the UNC Lineberger Comprehensive Cancer Center, NC Policy Collaboratory and UNC Center for Environmental Health and Susceptibility and was held at the UNC Lineberger Comprehensive Cancer Center in Chapel Hill, NC on May 13, 2019.

The panel members included:

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Panel Chair

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Overview

Fully understanding the basis of the elevated rates of thyroid cancer in Iredell County and other parts of North Carolina (NC) represents a complex problem. Currently, the etiology (cause) of thyroid cancer remains poorly understood. The only established modifiable risk factors include ionizing radiation exposure in childhood and obesity (2-3). A well-known increase in thyroid cancer in the US and elsewhere has been largely attributed to increased screening and medical surveillance (4-6). Disentangling this phenomenon from other underlying risk factors such as environmental exposures, lifestyle factors, and other health factors is exceedingly challenging, often at the limits of epidemiologic, statistical, and environmental study design and assessment methods.

In this context, the panel considered multiple research approaches that would inform understanding of the elevated rates of thyroid cancer in Iredell County and other parts of NC. After considering current scientific evidence and methodologies, the panel identified several additional analyses, exchanges of information, available data resources, and possibly new studies that have the potential to provide new insights into this complex problem. Some of the recommendations also provide a roadmap to improve surveillance of thyroid cancer and develop new analytical approaches for future analyses of thyroid and other cancers in NC.

We present 10 recommendations, organized by the type of activity, including new resource development, expansion of current projects and analyses, and application of new methods, enhanced infrastructure, and increased collaborations. Resources needed to implement these recommendations vary, from modest investments for analyzing existing data to significant funds needed to mount a NC patient study. The recommendations, depending on the specific activity, can be implemented through partnerships of different organizations, inside and outside NC, including the NC DHHS, academic institutions, federal organizations, and with other state health departments.

Recommendations

I. Leveraging New Data Resources

- **Develop NC thyroid cancer patient study.**

To gather new data on potential factors involved in the occurrence of thyroid cancer in NC, a population-based case series or case-control study could be performed. The study would systematically identify patients from selected areas of NC with elevated rates of papillary thyroid cancer (PTC) and selected areas without elevated rates. Data could be collected on medical providers and environmental, lifestyle, or other factors through a survey, biospecimen collection, and household environmental sampling. The study would help to map networks of health care and identify patterns of symptomatic/asymptomatic disease, as well as serve as a resource for future etiologic investigations. The study would have retrospective and prospective phases.

To conduct such a study, the UNC Lineberger Comprehensive Cancer Center Rapid Ascertainment Core would identify cases diagnosed in the study areas in the last two years, and new cases would be identified over a 2-year period. Pathology reports for each case would be obtained, and physician permission would be obtained to contact patients. The survey would be based on the questionnaire used in the Duke-Iredell community study. An in-person interview

also would include a blood draw and household dust sampling to assess environmental exposures. Cases also would be consented for release of all relevant medical records and permission to link with health care claims data, and to obtain a sample of their tumor. Study staff would work with hospitals and clinics to obtain a representative tumor sample for future molecular analysis to identify potential mutations that are associated with specific exposures, such as radiation. Medical records would be obtained and the cases' interaction with the health care system mapped to identify the potential contribution or non-contribution of physician practice patterns to disease detection in people who presented without symptoms. To fully explore certain risk factor hypotheses, a control group of individuals without thyroid cancer would be needed.

- **Analyze health care claims data to better understand clinical practice and detection patterns.**

Identifying areas where there is a high intensity of medical practice can provide insights into the potential contribution of medical surveillance to rates of thyroid cancer diagnosis. The more people receiving services that lead to the identification of thyroid cancer, the more likely it is that rates in the area may be higher. For this reason, the panel recommends further examination of the activities and people that are in the pathway to diagnosis. Overall rates (per 100,000 Medicare beneficiaries) of thyroid needle biopsy, thyroid ultrasound and thyroid surgery are the most proximal activities to analyze. A potential approach would be to adapt the Dartmouth Atlas methodology (7). Looking at the full set of available health care claims, this method uses a technique commonly known as small area analysis, which is population-based. Small area analysis focuses on the experience of the population living in a defined geographic area or the population that uses a specific hospital. In this approach, the utilization is mapped by hospital service areas (HSAs) or hospital referral regions (HRRs), which are local health care markets for hospital care. An HSA is a collection of ZIP codes whose residents receive most of their hospitalizations from the hospitals in that area. Both the HSA's and HRR's have been mapped for the entire U.S. and are available from Dartmouth for free (7), as are crosswalks to ZIP codes, which would enable comparison with rates of thyroid cancer from the registries. This approach may provide clues to the underlying geographic and time-based patterns. Claims data do have limitations; more granular individual data on symptoms and diagnostic approaches enables these limitations to be overcome by mapping individual patient interactions with the health system as described in the preceding recommendation.

- **Analyze health care claims data for benign thyroid disease patterns.**

Several types of benign thyroid diseases, such as the presence of thyroid nodules, goiter, and hyperthyroidism, are strongly associated with PTC. Therefore, it would be helpful to understand whether there are geographical variations in the rates of diagnosis of these diseases that correlate or overlap with areas of elevated PTC. This analysis may be valuable to assess potential shared risk factors, such as environmental or medical detection factors. Health care claims data can be used as one source to estimate rates of diagnosis of benign thyroid diseases by insurance coverage and county.

It also may be useful to compare rates of diagnosis for benign structural thyroid disease (particularly small goiters, nodules, and adenoma) across counties, stratified on insurance coverage type, because these diseases would be diagnosed in a medical encounter but might not otherwise cause symptoms. If increased medical surveillance accounts for some of the

portion of the geographic variation in the incidence of PTC, we also would expect to observe elevated incidence rates of mild benign structural thyroid disease in the counties that have elevated incidence rates of PTC.

Similarly, the rates and patterns of functional thyroid disease, such as hypo or hyperthyroidism, might reflect some portion of cases that have shared environmental risk factors with thyroid cancer; however, diagnostic work-up and treatment of functional diseases also can lead to incidental detection of thyroid cancer.

These analyses using claims data have some challenges including the potential for missing information on insurance coverage by county, lack of details about benign thyroid disease severity, and the need to control tightly for differences in age. Other challenges include the lack of complete lifetime medical history information and other potential individual-level confounders. Moreover, some of the patients in the database are expected to change residences between counties and in and outside of the state and/or change insurance coverage, potentially obscuring the results to some extent. Thus, the results of such an effort would need to be interpreted cautiously.

- **Leverage existing data from epidemiologic cohort studies to inform the NC situation.**

Investigation of regions with relatively high incidence rates of thyroid cancer can stimulate new hypotheses regarding lifestyle or environmental risk factors that may be contributing to the occurrence of the disease. Ideally, these hypotheses can be tested in well-powered, well-designed epidemiologic studies. Depending on the hypothesis, these studies do not always need to be conducted in the same region as the high-incidence area if the initial findings appear to be generalizable. Research on potential risk factors for thyroid cancer is currently being conducted by experts around the world using cohort studies, such as the ones listed in Appendix A and on the NCI Cohort Consortium website (<https://epi.grants.cancer.gov/Consortia/cohort.html>). Prospective cohort studies are characterized by the collection of individual-level exposure from persons who are free of the outcome of interest and are then followed over time for that outcome. Case-control studies in which the exposure history of those with thyroid cancer is retrospectively obtained and compared to those without cancer are particularly valuable in populations with higher incidence rates and/or unique exposures. Some ongoing cohort studies include cancer-free individuals and thyroid cancer survivors residing in North Carolina; these are noted in Appendix A.

The panel recommends that in the future these cohorts be considered as a valuable platform to test hypotheses generated from investigations in NC. We also encourage examination of exposure of interest using data from cohort studies that include participants from NC. Prioritization is still with focused, well-designed investigations in NC, but we believe that using available data provides a valuable second stage of confirmatory research.

II. Expanding Ongoing Analyses

- **Investigate potential associations between exposure to coal ash, coal burning emissions, and papillary thyroid cancer.**

Given community concerns regarding exposure to coal ash in NC and its potential health effects, the panel recommends investigating associations between exposure to coal burning activities, including coal ash, and papillary thyroid cancer (PTC). This investigation based on research being conducted at Duke University, could be implemented using a case-control study design in which exposure to specific metals or radionuclides associated with coal ash could be examined in patients with PTC relative to controls without PTC sampled from the same source population. However, it would be important that the case-control design account for potential confounding factors, including childhood radiation exposure, obesity, smoking rates, age, sex, race, other socioeconomic indicators, tumor characteristics, and family history of thyroid disease. Exposure pathways to consider should include ingestion (e.g., via contaminated drinking water) and inhalation. Given the long timeframe for development of cancer, a limitation of this approach is the assumption that current exposure levels are representative of historical levels, which are more relevant for understanding factors involved in the etiology of the disease. One approach to address this limitation may be to investigate contaminant levels reported in archived public utility water reports based on water districts.

- **Conduct geospatial analysis of thyroid cancer in states neighboring NC.**

Assessing spatial patterns of disease can be useful in generating hypotheses for further research aimed at understanding the variables contributing to cancer etiology. However, evaluating patterns at the county or ZIP code level can be challenging, particularly given that population size can change within a short time period and case numbers are small. This dynamic has been particularly challenging when estimating PTC incidence rates in North Carolina (NC), where concerns regarding higher PTC rates were reported in Iredell County. One approach to addressing this challenge is to estimate the proportion of PTC within all cancers and then evaluate how the proportions change over time.

For example, Drs. Kate Hoffman and Heather Stapleton (Duke University) conducted a series of spatial analyses using generalized additive models (GAMs) to predict the odds of PTC across the entire state, using geocoded residential locations for all cancers recorded between 2001-2017 in the NC Central Cancer Registry. Results of these analyses highlighted areas with higher odds of PTC relative to all cancers. Of note, several regions of NC, including Iredell, Rowan, New Hanover, and Brunswick counties displayed statistically significantly elevated odds of PTC. However, in some cases, the regions of NC with elevated odds of PTC changed over time, suggesting that some risk factors might have changed over time. Additionally, some areas bordered the state line. Due to the constraints of the statistical model, it is difficult to determine how accurate the results are for the state borders. To overcome this limitation, the panel recommends that a similar geospatial analysis be conducted using state cancer registry data for Virginia, Tennessee, and South Carolina. This analysis would provide insight into whether the higher rates of PTC observed near the state border are observed using the other cancer registry databases. Having access to a larger catchment area to conduct this geospatial analysis of PTC also would help develop research hypotheses that could be investigated in the future and help identify risk factors for PTC.

- **Conduct comparative analysis of other cancers in Iredell county and other NC counties with elevated rates of thyroid cancer**

To determine if other cancers have elevated rates in the same areas with an excess of thyroid cancer, additional description of rates and trends should be conducted. Rates of cancers that are screening-related, such as prostate and breast cancer, will offer context for a comparison with thyroid cancer by providing an indirect measure of engagement with the healthcare system and health care access. The panel also recommends that analyses be conducted to examine major cancer risk factors (such as obesity, smoking) by NC county. These analyses can help generate hypotheses about specific factors, environmental and non-environmental, that may be influencing the incidence of other cancers. These data are available from multiple public data sources such as the Behavioral Risk Factor Surveillance System (BRFSS, 8).

III. Methods, Infrastructure Enhancement, and Collaborations

- **Host a workshop to consult with local and national experts on rate and geospatial analysis methods.**

Analysis of state and regional cancer rates, trends, patterns, and associations with environmental and other factors is complex. Factors that introduce complexity include defining the area of study, assessing random error, selecting models for geospatial analysis, and determining associations with environmental and other factors. The comprehensive analysis of rates and trends in NC cancer data would benefit from a workshop including experts from the NC DHHS, NC universities, and national experts. The workshop would help with current thyroid cancer analyses in Iredell and other NC counties and support future investigation of other cancers in NC. The workshop could provide additional methodologic approaches, tools and examples that could be applied to NC cancer data. The workshop could also include analysts from other states (see recommendation below).

- **Enhance NC Central Cancer Registry's case ascertainment and staging of thyroid cancer.**

Thyroid cancer data collected by the NC Central Cancer Registry (NC CCR) is of the highest quality. The NC CCR is well-regarded, earning the CDC's highest level of recognition from the CDC National Program of Cancer Registries for meeting the standards for Data Completeness and Quality. Additional resources should be provided to continue to ensure the quality and completeness of the registry data, including details of tumor size and extent of spread, and to enhance timeliness of reporting. It should be noted that physicians' offices play an important role in reporting cases to the CCR and improving the consistency of this reporting would ensure more complete data and better surveillance. Physicians should be encouraged to provide timely and consistent reporting of cancer cases to the cancer registry.

- **Increase collaboration with epidemiologists in other states who have investigated elevated cancer rates.**

Because elevated rates and clusters of cancer have been documented in counties of other states, the panel recommends that epidemiologists and other scientists from NC and other states confer regarding findings and challenges and consider information and methods exchanges and potential joint investigations.

Appendix A

Examples of Large Epidemiologic Cohort Studies with Follow-up for Cancer Incidence, including Thyroid Cancer

Study name	Population size (n)	Biospecimens collected at baseline (blood, urine, toenails, other)?
Adventist Health Study-2*	95,000	No (possibly in small subsets)
Agricultural Health Study*	65,000	No
California Teachers Study	133,000	No (blood collected ~12% between 2013-16)
Cancer Prevention Study-II*	185,000	Yes (blood, on ~70,000)
European Prospective Investigation into Cancer and Nutrition	500,000	Yes (blood)
Health Professionals Follow-up Study**	52,000	Yes (blood)
Iowa Women's Health Study	42,000	No
Multiethnic Cohort Study	215,000	Yes (blood and urine on ~30%, 5-10 years after baseline)
NIH-AARP Diet and Health Study*	500,000	No
Nurses' Health Study	120,000	Yes (toenails on ~50,000 in 1982-4, blood on ~30% in 1989-90, second blood and urine on ~16% in 2001-4)
Nurses' Health Study-2*	116,000	Yes (similar design as NHS)
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Study	150,000	Yes (blood, on ~50%)
Shanghai Women's Health Study	75,000	Yes (blood and urine)
Southern Community Cohort Study*	85,000	Yes (blood on ~45%, urine on ~37%)

Sister Study*	50,000	Yes (blood, urine, toenails, dust)
Southern Community Cohort Study*	85,000	Yes (blood on ~45%, urine on ~37%)
U.S. Radiologic Technologists Study*	110,000	No (post-diagnostic blood collected for thyroid cancer cases and controls)
Vitamins and Lifestyle Study	77,000	No
Women's Health Initiative*	94,000	Yes (blood)
Women's Health Study**	40,000	Yes (blood)

*Includes participants from North Carolina who were free of cancer at study entry and were followed over time for a diagnosis of cancer.

**Unknown whether any of the participants resided in North Carolina at study entry. Additional information could be obtained from the Principal Investigator of the cohort.

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