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Combating gastric cancer in Alaska Native people: An expert and community symposium

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Summary of Problem

Alaska Native (AN) people experience higher incidence of, and mortality from, gastric cancer compared to other U.S. populations[1, 2]. Compared to the general U.S. population, gastric cancer in AN people occurs at a younger age, is diagnosed at later stages, is more evenly distributed between the sexes, and is more frequently signet-ring or diffuse histology[3]. It is known that the prevalence of *Helicobacter pylori* (*Hp*) infection, a risk factor for gastric cancer, is high in AN people[4]; however, high antimicrobial resistance combined with high reinfection rates in Alaska make treatment at the population level complex[5]. In addition, health issues in AN people are uniquely challenging due to the extremely remote locations of many residents.

A multiagency workgroup hosted a symposium in Anchorage that brought internationally-recognized experts and local leaders together to evaluate issues around gastric cancer in the AN population. The overall goal of this symposium was to identify the best strategies to combat gastric cancer in the AN population through prevention and early diagnosis.

Symposium Framework

In order to identify goals and actions that were scientifically sound, logistically realistic, and culturally acceptable, a symposium was hosted in Anchorage, Alaska in July 2019. This symposium brought together voices from many viewpoints, included gastric cancer and *Hp* experts, Alaskan health providers, AN community and tribal leaders, public health officials, and representatives from other North American Indigenous populations. Overall, 57 people attended and contributed to this symposium.

The symposium aimed to identify concrete actions and was designed to maximize discussion. Scientific presentations were kept to a minimum. Presenters were encouraged to present well-established conclusions and information that could be used to address gastric cancer in AN people. After the scientific presentations, the symposium was divided into small groups and participants were asked to identify the main questions or challenges related to gastric cancer in AN people. On the second day, the group was divided into two sections; one focused on scientific data and investigations, and one focused on community priorities and cultural acceptability. The symposium ended with the two groups coming together to summarize findings. The overall goal of this symposium was not to create guidance but to

evaluate existing data, identify knowledge gaps, and summarize actions that could improve gastric cancer diagnosis and survival.

Brief Introduction to the Alaska Native Population and Health System

Alaska covers 17% of the land area of the United States, but has only 0.2% of the population. The population is very dispersed and often difficult to reach, as only 14% of municipalities are connected to a road system. Many communities depend on single engine airplanes for transportation to health care facilities. AN people make up 15% of the Alaska population; 50% of whom live outside of an urban center, often in crowded homes that lack running water[6]. Health care for the AN people is provided through tribally owned and managed health organizations.

Scientific Presentations

Gastric Cancer in Alaska

The epidemiology of gastric cancer among the AN population differs from that of other populations in the United States and other high-income countries; occurring at a younger age and more evenly divided between male and female[3]. Mortality is higher, with 50% of cancers diagnosed at a metastatic stage[3]. Histologically, gastric cancer in the AN population is more frequently non-cardia, diffuse, and signet-ring cell subtype when compared to gastric cancer typically reported in high income countries [3]. In addition, 30% of AN individuals with gastric cancer have a family member who has been diagnosed with a gastrointestinal malignancy, higher than what is reported in other populations[2, 3, 7]. The pattern of gastric cancer in Indigenous Canadians and the Maori of New Zealand is similar to that in the AN population, with cancer occurring at higher rates in younger people and in women compared to their majority populations, and with a higher proportion diffuse and non-cardia in location[8, 9]. Esophagogastroduodenoscopy (EGD) performed in Canadian Arctic communities found a high prevalence of severe gastritis and atrophy[10], though treatment of *H. pylori* (*Hp*) was generally successful and antimicrobial resistance was lower than seen in Alaska.

In the year preceding the symposium, a number of AN persons under 18 years old were diagnosed with gastric cancer, all of whom had stage IV, signet ring cell carcinomas. This rate is 7.1 cases per 100,000 people aged 15 to 20 years—dramatically higher than the age adjusted rate reported by the National Cancer Institute in the overall United States for the same age group (0.1 per 100,000)[11]. In contrast, only five minors were diagnosed with gastric cancer over an 18-year period at a large cancer referral center in Texas [12].

Esophagogastroduodenoscopy (EGD) in Alaska

Current U.S. gastroenterology guidelines do not endorse endoscopic screening for gastric cancer due to the overall low incidence in the United States. Approximately 3,000 EGDs are performed each year within the Alaska Tribal Health system. In a study of 200 patients, 70% had gastritis, 12% had gastric ulcers, 3% had duodenal ulcers, 12% had intestinal metaplasia, and 65% were positive on histology for *Hp*[13, 14].

Helicobacter pylori

Data from Alaska have shown very high rates of *Hp* antimicrobial resistance and treatment failure[15]. A study that evaluated re-infection with *Hp* in AN people after successful treatment found that 22% of AN people in rural areas were re-infected by 2 years [5] and >35% by 12 years (unpublished data), a rate much higher than reported in other populations in developed countries. Broad *Hp* treatment across the population is associated with risks, including overall changes to the host microbiome, increased antimicrobial resistance, and possible immunologic changes[16]. An Arctic-specific consensus statement on *Hp* management recommended *Hp* evaluation and treatment only in persons with specific pathology to avoid increasing antimicrobial resistance and adverse events[17].

Gastric Cancer Screening Programs in Japan and Korea

While no gastric cancer screening guidelines exist in the United States, both Korea and Japan have population level screening programs. The rates of gastric cancer in the AN population (22.4 cases per 100,000 people)[18] are closer to those of the Republic of Korea (34.0/100,000) and Japan (27.5/100,000)[19]. The national screening program in Korea targets people over 40 years of age, while Japan targets people over 50 years. Japan has seen an overall decrease in gastric cancer rates [20], at least partially due to the decreased prevalence of *Hp* infection in Japan after World War II[21]. Since the Korean screening program began, gastric cancer mortality decreased by 21% in all ages and 47% among people 40–74 years of age [22]. Screening via EGD is cost-effective in Korea and is preferred over upper gastrointestinal series [23].

Molecular characterization of gastric cancer

Gastric cancer is divided into four molecular subtypes[24], which show different genomic patterns, ranging from hypomethylation to hypermutation and aneuploidy. In-depth analysis of the *CDH1* gene, a mutation known to be related to familial diffuse gastric cancer, has found that the type of mutation was related to the age of gastric cancer diagnosis in the general population. To our knowledge, no mutations in *CDH1* have been identified in AN gastric cancer patients.

Simulation modeling in gastric cancer

Simulation modeling has been used to answer questions about cancer interventions, including the cost effectiveness of an intervention and the overall risk to a population as underlying risk factors change. Models have been created to evaluate the benefit of EGD screening in China and Colombia, considering the value of screening by EGD versus serum pepsinogen or *Hp* antibody level[25].

Discussion Sections

Scientific Panel

The members of the scientific panel evaluated the gastric cancer epidemiology in AN people in the context of world-wide data. There was substantial concern about the recent gastric cancer cases in teenagers, as this has not been seen in other populations. Individuals in this

group noted that most data about gastric cancer pathogenesis and screening comes from work on intestinal-type gastric cancer, and, therefore, may not be applicable to the diffuse-type that is more common in the AN population. With this limitation in mind, this panel reviewed the data gaps and areas for improvement.

The members of the scientific panel had an extensive discussion regarding the high prevalence of *Hp* infection in the AN population. It was felt that, in this population, the potential risks and costs were too high to make *Hp* elimination beneficial. Instead, focused *Hp* treatment in individuals with high-risk gastric pathology or a family history of gastric cancer was deemed more appropriate.

Community Panel

The members of community panel recognized the value of the Japanese and Korean screening programs; however, felt they would be difficult to implement in Alaska. Instead, they thought EGDs targeting people at high risk and improving the ability to identify those at high risk would be most valuable. Community providers were extremely concerned that wide-spread *Hp* treatment would lead to higher antibiotic resistance.

Individuals in the community panel discussed the risk factors related to gastric cancer extensively, noting the high prevalence among AN of known risk factors, such as smoking, dental disease, *Hp* infection, and consumption of salted and smoked foods. However, they thought more information was needed about the risks associated with the lack of running water in homes, adverse childhood experiences, exposure to ground contaminants, and iq'mik, a homemade chew commonly used in some regions of Alaska that mixes tobacco with fungus ash.

The members of the community panel also thought additional education for communities was needed to increase understanding of gastric cancer, risk factors, and the benefits of screening. Participants suggested recruiting AN people to become genetic counselors, so that counselors are available to the AN community who are familiar with the cultural values and traditions.

Knowledge Gaps

Symposium participants identified a number of knowledge gaps:

1. What are the genetic, dietary, environmental, and behavioral risk factors for gastric cancer in the AN population?
2. Which people within the AN population would benefit from EGD screening?
3. What is the best way to detect diffuse gastric cancer in its early stages and how effective is endoscopy?
4. Why are some AN people developing gastric cancer at very young ages?
5. What is the current epidemiology of *Hp* infection in the AN population?

Overall Summary

Symposium participants voiced support for ongoing activities that address risk factors for gastric cancer, including promoting tobacco cessation, a healthy diet, dental hygiene, reduced alcohol use, and reduced salt intake.

Specific programmatic updates included the following: First, protocols followed by remote care providers could reinforce early referral of patients with a family history of gastric cancer or alarm symptoms for gastric cancer. Second, a state-wide upper endoscopy protocol could be developed that sets parameters for biopsy sampling based on the updated Sydney Protocol. Third, specialized training is needed for pathologists and endoscopists to enhance their ability to detect gastric cancer and to standardize diagnosis across the state. Fourth, a clinical guidelines committee could convene to examine current local *Hp* clinical guidelines and consider EGD screening of all individuals who have a first-degree relative with gastric cancer.

Clinical actions included a screening program for high-risk individuals. Specifically, first-degree relatives of gastric cancer patients and people diagnosed with gastric intestinal metaplasia could be enrolled in a program that includes surveillance EGDs and, if infection is present, *Hp* treatment. It was also recommended that when a case of gastric cancer is identified, community education be offered regarding gastric cancer prevention and screening.

Scientific projects could enhance the understanding of gastric cancer in the AN population. An existing collaboration with Canada to perform whole genome sequencing of *Hp* isolates to identify prevalent strains and their pathogenicity factors was considered to be highly valuable. Further investigation into markers of gastric cancer is needed, including comprehensive genomic analysis, characterization of non-invasive biomarkers, evaluation of tumor EBV expression, and assessment of tumor inflammatory cell infiltrate.

Risk stratification was identified as one of the most important areas for research. The group discussed initiating a study to evaluate risk-stratification techniques. First, a risk-stratification questionnaire could be developed and administered to people undergoing standard EGDs to determine if any demographic or lifestyle factors predict gastric pathology. Future studies might evaluate the predictive abilities of dietary questionnaires, microbiome composition, *Hp* genetics, EBV tumor status, urine salt and nitrate level, as well as serum pepsinogen, gastrin, and anti-parietal cell antibody levels.

Further evaluation of *Hp* infection epidemiology in AN communities was thought to be warranted. Specifically, the prevalence, acquisition, and transmission of *Hp* in children under the age of 5 years old is needed to understand the impact of sanitation and water systems on *Hp* infection. In addition, a study evaluating the impact of dental caries treatment in concert with *Hp* treatment was discussed.

Finally, it was suggested that newly diagnosed gastric cancer patients and their families be enrolled in studies designed to evaluate risk factors. Samples from patients and family

members should be collected and analyzed for known markers of gastric cancer and stored so that additional studies can be performed as new tests are developed.

Actions Discouraged

Participants concluded that broad *Hp* screening and treatment would not be beneficial. Given the high prevalence of *Hp* infection, it was thought that such a program was untenable due to logistical challenges, antibiotic resistance, and high reinfection rates. In addition, there was substantial concern about adverse impacts such as development of antibiotic resistance in other organisms, disruption of the microbiome, and other potential unintended consequences.

In addition, a statewide EGD screening program similar to those in Japan and Korea was thought to be logistically, economically, and culturally unrealistic. While EGD is one of the best methods for early gastric cancer detection, it is limited in its ability to identify diffuse gastric cancer; therefore, population-wide screening may be less beneficial in the AN population than in east Asian countries. Instead, the individuals at highest risk should be prioritized for screening.

Conclusion

This symposium combined scientific and community knowledge. Key discussions included implementing clinical and community education, targeted screening and surveillance within clinical practice, as well as basic science and epidemiologic investigations. While the pattern of gastric cancer in the AN population is different than what is typically seen in the United States and other high-income countries, it is similar to what is seen in other indigenous populations. This symposium report aims to share our overall symposium design and disseminate the evidence considered, the knowledge gaps identified, and the conclusions with others who are considering approaches to combat gastric cancer.

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Abbreviations

AN	Alaska Native
Hp	Helicobacter pylori
EGD	Esophagogastroduodenoscopy

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