Potentially preventable cancers diagnosed among Alaska Native people

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ABSTRACT

Cancer is the leading cause of death among Alaska Native (AN) people, and the third leading cause of years of potential life lost. AN tribal health leaders and researchers want to understand the cancer burden attributable to modifiable risk factors among AN people to inform the design of cancer prevention strategies. To address this question, we estimated the population attributable risk (PAR) associated with modifiable cancer risk factors including obesity, smoking, physical inactivity, and alcohol use among AN people. PAR varied by cancer site and risk factor, and was highest for lung cancer and smoking, with an estimated 78.8% of cancers among males, and 69.8% among females attributable to this risk factor. A smaller, but still substantial proportion of cancers were associated with obesity (up to 37% for endometrial cancer among females), physical inactivity (up to 18% for endometrial cancer among females), and alcohol use (up to 34% for breast cancers among heavy drinking females). Overall, we estimated that approximately 1500 cancers could be prevented over a 10-year period if these four risk factors were eliminated among AN people. This study demonstrates the importance of smoking as a primary prevention target to reduce the burden of cancer and other chronic diseases among AN people. However, it also indicates that obesity, physical activity, and alcohol use may account for a varying, but substantial proportion of cancers in this population. Given the high burden of cancer among AN people, a comprehensive approach to primary prevention is warranted..

KEYWORDS: Native American, population attributable risk, cancer prevention

Citation: Nash SH and Redwood DG (2017).Potentially preventable cancers diagnosed among Alaska Native people. Cancer Health Disparities 2:e1-e15. doi:10.9777/chd.2018.10001

INTRODUCTION

Cancer is the leading cause of death among Alaska Native (AN) people, and the third leading cause of years of potential life lost (Alaska Native Epidemiology Center, 2017; Blake, 2016; Carmack, 2015). In contrast to U.S. whites (USW), for whom cancer incidence and mortality rates have been significantly declining over the past 20+ years (Ryerson et al., 2016), rates remained fairly constant among Alaska Native people, resulting in a significant health disparity (Blake, 2016; Carmack, 2015). Furthermore, disparities in incidence of several cancer sites exist between AN people and USW, including lung, colorectal, and nasopharyngeal cancers, which are 1.5, 2.3, and 17.3 times higher among AN people than USW, respectively (Carmack, 2015; Kelly JJ et al., 2014). For these reasons, cancer is a leading concern among Alaska tribal health leaders and researchers, and the Alaska Native Tribal Health Consortium's (ANTHC) Cancer Program has developed a Comprehensive Cancer Control Plan (CCCP) specifically for the Alaska Tribal Health System (ATHS) (2006).

Reducing the burden of cancer among AN people may be achieved through a focus on cancer prevention. It has been estimated that upwards of 50% of cancer deaths globally may be preventable (Colditz et al., 2006; Colditz and Wei, 2012), and a growing number of cancers are known to have risk factors that are potentially modifiable (Stein and Colditz, 2004). These include some of the leading cancer sites among Alaska Native people: female breast, lung, colorectal, and prostate cancers (Carmack, 2015). Leading modifiable risk factors for cancer include tobacco use, alcohol use, diet, infectious diseases, obesity, and physical inactivity (Siegel et al., 2017; Stein and Colditz, 2004). Little is known about the burden of potentially preventable cancers among AN people. Yet, AN people do not meet national recommendations for many modifiable cancer risk factors, including tobacco use, overweight and obesity, and fruit and vegetable consumption (Lanier et al., 2012). There is a critical need to better understand modifiable risk factors for cancer among AN people, and the burden of potentially preventable cancers. The potential contribution of modifiable risk factors to cancer burden can be assessed using population attributable risk (PAR). This study analyzed the PAR associated with modifiable risk factors for cancer among AN people, including obesity, smoking, physical inactivity, and alcohol use.

MATERIALS AND METHODS

Study population

American Indian and Alaska Native people (AI/AN) represent a diverse group indigenous to North America. The Alaska Department of Labor estimated that in 2014, 143,367 AI/AN people (alone or in combination) resided in Alaska, accounting for 19% of the total Alaska population (Alaska Department of Labor and Workforce Development, 2015). There are 229 federally recognized tribes in Alaska (American Congress of American Indians, 2017; Williams, 2009).

The Alaska Tribal Health System (ATHS) is made up of over 14 regional tribal health organizations, which provide health care services, including health promotion and disease prevention programs, to all AI/AN beneficiaries living in Alaska. The Alaska Native Tribal Health Consortium (ANTHC), a consortium of regional tribal health organizations, provides statewide health services, and co-manages Alaska's only tertiary tribal healthcare facility, the Alaska Native Medical Center (ANMC) located in Anchorage.

Cancer Sites

We estimated PAR for all cancer sites known to be associated with smoking, obesity, physical inactivity, or alcohol use. Smoking-related cancers were those determined by the 2014 Surgeon General's report to be causally linked to smoking, and included acute myeloid leukemia (AML), as well as cancers of the bladder, colon and rectum, esophagus, kidney, larynx, liver, lung, oral cavity, pancreas, stomach, and uterine cervix (Alberg et al., 2014). Obesity-related cancers were those determined by the World Cancer Research Fund/American Institute for Cancer Research to be associated with obesity (Wiseman, 2008), including cancers of the esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, postmenopausal breast, kidney, advanced prostate, thyroid, and endometrium. Physical inactivity-related cancers were those determined by a recent systematic review and meta-analysis to be convincingly or probably associated with physical activity or inactivity (Friedenreich et al., 2010), and included cancers of the colon, lung, prostate, breast, endometrium, and ovaries. Finally, alcohol-related cancers were those determined by a recent systematic review and meta-analysis to be statistically significantly associated with moderate, or heavy drinking (Bagnardi et al., 2015), including cancers of the colon and rectum, esophagus (squamous cell carcinoma (ICD-O histologies 8070-8076) only), gallbladder, larynx, liver, lung, oral cavity, stomach, prostate, and breast.

Data sources and definitions

Prevalence of cancer risk factors among Alaska Native people was estimated using data from the Alaska Behavioral Risk Factor Surveillance Survey (BRFSS), collected by the Alaska Department of Health and Social Services, Division of Public Health, and the Centers for Disease Control and Prevention. Data reported are for the 5-year period 2011-2015, unless otherwise noted. Individuals were defined as current smokers if they reported having smoked more than 100 cigarettes in their lifetime, and also reported current smoking. Obesity was defined according to World Health Organization (WHO) guidelines as having a body mass index (BMI) ≥ 30 kg/m^2. Physical inactivity was defined as not meeting the CDC-recommended 150 minute/week of aerobic activity (Centers for Disease Control and Prevention, 2008). Information on physical activity was available from the 2011, 2013, and 2015 BRFSS surveys only. Alcohol intake (g ethanol/day) was estimated as (average number of drinks/day*g ethanol/drink). We estimated that each drink contained 12.5 g ethanol (Bagnardi et al., 2015). We categorized moderate and heavy drinking as 12.5 ≤ 50 g/d (4 drinks/d) and >50 g/d (4 drinks/d), respectively, as per a recent review and meta-analysis (Bagnardi et al., 2015).

Cancer case counts were from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program's Alaska Native Tumor Registry (ANTR). The ANTR is a population-based registry that records cancer information on AI/AN people who meet eligibility requirements for Indian Health Service benefits, who have been diagnosed with cancer in the state of Alaska, and who are Alaskan residents at the time of cancer diagnosis. As part of the ANTR's standard surveillance process for collecting SEER data, cases were identified through a variety of sources, including: tumor registry and pathology files of ANMC and other Native and non-Native healthcare facilities throughout the state; linkage to the Alaska State Cancer Registry and the Washington State Cancer Registry; and death certificates (<1% cases). For this study we used data on the number of cancers diagnosed between January 1, 2006 and December 31, 2015.

Classification of cancer site of origin, histologic cell type, behavior and grade coding followed the *International Classification of Diseases for Oncology* (ICD-O) third edition (2013). We included only invasive malignancies (ICD-O behavior code 3); benign and in situ tumors were not included in case counts (ICD-O behavior codes 0 and 2, respectively), nor were tumors of uncertain or unknown behavior (ICD-O behavior code 1). Menopausal status was not available through the registry; therefore, age at diagnosis (< 50y, ≥50 y) was used as a proxy to define post-menopausal breast cancer. Advanced prostate cancer was defined by having an AJCC stage group (7th edition; ref) of III or IV, or a Derived Summary Stage 2000 of "Distant."

Table 1. Relative risk of cancer associated with each cancer site, and modifiable risk factor, used herein to estimate population attributable risk.[a-d]

Cancer Site	Smoking		Obesity		Physical Inactivity		Moderate alcohol use		Heavy alcohol use	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Acute Myeloid Leukemia	1.09	1.09	--	--	--	--	--	--	--	--
Bladder	3.14	3.14	--	--	--	--	--	--	--	--
Colorectal	1.19	1.28	--	--	--	--	1.21	1.07	1.53	1.24
Colon	--	--	1.45	1.12	1.32	1.32	--	--	--	--
Rectum	--	--	1.25	1.05	--	--	--	--	--	--
Esophagus	2.52	2.28	1.12	1.06	--	--	--	--	--	--
Esophageal SCC	--	--	--	--	--	--	2.23	2.23	4.95	4.95
Gallbladder	--	--	1.54	1.75	--	--	--	--	2.64	2.64
Kidney and Renal Pelvis	1.59	1.35	1.59	1.91	--	--	--	--	--	--
Larynx	6.98	6.98	--	--	--	--	1.44	1.44	2.65	2.65
Liver	1.85	1.49	1.99	1.43	--	--	--	--	2.07	2.7
Lung	9.87	7.58	--	--	1.43	1.43	--	--	--	--
Oral Cavity	3.43	3.43	--	--	--	--	1.83	1.83	5.13	5.13
Pancreas	1.63	1.73	1.45	1.28	--	--	--	--	--	--
Stomach	1.74	1.45	1.11	1	--	--	--	--	--	--
Thyroid	--	--	1.14	1.26	--	--	--	--	--	--
Male only										
Prostate	--	--	--	--	1.25	--	--	--	--	--
Advanced prostate	--	--	1.15	--	--	--	--	--	--	--
Female only										
Breast	--	--	--	--	--	1.33	--	1.23	--	1.61
Postmenopausal breast	--	--	--	1.16	--	--	--	--	--	--
Endometrium	--	--	--	2.54	--	1.43	--	--	--	--
Ovarian	--	--	--	--	--	1.23	--	--	--	--

Uterine cervix	--	1.83	--	--	--	--	--	--	--	--

[a]Relative risk estimates for smoking taken from: Gandini et al Int J Cancer 2008: 122;155-164. Botteri et al JAMA 2008:300;2765-2778. [b]Relative risk estimates for obesity taken from Cheragi et al PLoS One 2012:7;e51446. Xue et al Eur J Cancer Prev 2016: *26*, 94-105. Jenabi et al Pub Health 2015:129;872-880. [c]Relative risk estimates for physical inactivity modified from Friedenreich et al Eur J Cancer 2010:46;2593-2604. [d]Relative risk estimates for alcohol use (moderate and heavy) taken from Bagnardi et al Br J Cancer 2015:112;580-593

Table 2. Prevalence of modifiable risk factors for cancer among Alaska Native people, Alaska Behavioral Risk Factor Surveillance System, 2011-2015.

	Obesity	Smoking	Physical Inactivity	Current drinking			
				Current drinking (yes)	Moderate (1-4 drinks/day)	Heavy (>4 drinks/day)	Average drinks/ day
Total	34.8 (33.0, 36.6)	37.7 (35.9, 39.5)	50.9 (47.4, 54.3)	42.4 (40.2, 44.7)	8.9 (7.7, 10.3)	10.4 (9.1, 11.8)	0.41 (0.36, 0.46)
Sex							
Male	31.6 (29.2, 34.0)	40.2 (37.6, 42.9)	49.8 (44.9, 54.8)	44.8 (41.5, 48.2)	12.0 (9.9, 14.4)	11.6 (9.8, 13.8)	0.56 (0.47, 0.66)
Female	38.4 (35.7, 41.1)	35.1 (32.6, 37.7)	51.9 (47.0, 56.7)	40.0 (36.9, 43.1)	5.8 (4.6, 7.3)	9.1 (7.4, 11.1)	0.25 (0.21, 0.29)
Age (yr)							
18-34	26.3 (23.4, 29.4)	42.2 (38.9, 45.5)	44.8 (38.8, 5.9)	45.3 (41.3, 49.5)	10.2 (7.9, 13.1)	11.1 (8.7, 14.0)	0.42 (0.33, 0.5)
35-49	42.4 (38.8, 46.0)	40.9 (37.4, 44.5)	53.5 (46.9, 60.1)	48.4 (44.1, 52.8)	10.7 (8.4, 13.4)	9.3 (7.2, 11.9)	0.54 (0.43, 0.66)
50-64	39.3 (36.0, 42.7)	35.9 (32.7, 39.2)	54.0 (47.8, 60.1)	37.6 (33.8, 41.5)	8.1 (6.0, 10.8)	8.6 (6.8, 10.8)	0.35 (0.27, 0.44)
65+	38.4 (33.7, 43.4)	17.0 (13.9, 20.6)	58.5 (47.8, 68.4)	30.4 (23.9, 37.9)	3.7 (2.5, 5.5)	12.0 (8.4, 16.8)	0.2 (0.14, 0.25)

Table 3. Population attributable risk (PAR) percent and estimated preventable cases (EPC) of cancers classified as associated with tobacco, obesity, and physical inactivity.

	Tobacco				Obesity				Physical inactivity			
	Male		Female		Male		Female		Male		Female	
	PAR	EPC	PAR	EPC	PAR	EPC	PAR	EPC	PAR	EPC	PAR	EPC
Acute Myeloid Leukemia	3.6	0.7	3.1	0.4	--	--	--	--	--	--	--	--
Bladder	47.3	16.1	42.9	7.7	--	--	--	--	--	--	--	--
Colorectal	7.3	25.2	8.9	30.9	--	--	--	--	--	--	--	--
Colon	--	--	--	--	12.6	42.9	4.4	15.1	13.6	29.8	14.1	35.9
Rectum	--	--	--	--	6.9	8.5	1.8	1.7	--	--	--	--
Esophagus	38.9	16	31	6.8	3.5	1.4	2.2	0.5	--	--	--	--
Gallbladder	--	--	--	--	13.9	0.4	22.2	1.8	--	--	--	--
Kidney and Renal Pelvis	19.8	22.0	10.9	10.0	15.0	16.7	25.7	23.4	--	--	--	--
Larynx	71.5	17.9	67.7	3.4	--	--	--	--	--	--	--	--
Liver	26.3	15.3	14.7	4.0	22.9	12.8	14	3.5	--	--	--	--
Lung	78.8	280.7	69.8	201.7	--	--	--	--	17.5	62.6	18.1	52.6
Oral Cavity	50.5	44.5	46	26.7	--	--	--	--	--	--	--	--
Pancreas	20.9	11.1	20.3	10.8	11.9	6.3	9.6	5.1	--	--	--	--
Stomach	23.7	24.9	13.6	9.8	3.2	3.4	--	--	--	--	--	--
Thyroid	--	--	--	--	4.0	1.1	9.0	7.8	--	--	--	--
Male only												
Prostate	--	--	--	--	--	--	--	--	11.1	22.7	--	--
Advanced prostate	--	--	--	--	4.3	1.6	--	--	--	--	--	--
Female only												
Breast	--	--	--	--	--	--	--	--	--	--	14.7	94.0
Postmenopausal breast	--	--	--	--	--	--	5.7	26.9	--	--	--	--
Endometrium	--	--	--	--	--	--	36.9	29.9	--	--	18.1	14.6

Ovarian	--	--	--	--	--	--	--	--	--	--	10.9	5.5
Uterine cervix	--	--	22.6	13.3	--	--	--	--	--	--	--	--
Total		474.4		325.5		95.1		115.7		115.1		202.6

[a]EPC for a 10-year period, calculated using the number of cancers diagnosed among AN people for the 10-year period from 2006-2015.

Table 4. Population attributable risk (PAR) percent and estimated preventable cases (EPC) of cancers classified as associated with moderate and heavy alcohol use.

	Moderate drinking				Heavy drinking			
	Males		Females		Males		Females	
Cancer site	PAR	EPC	PAR	EPC	PAR	EPC	PAR	EPC
Colorectal	2.5	8.4	0.4	1.4	5.8	19.8	2.1	7.4
Esophageal SCC	12.9	3.5	6.7	0.5	31.4	8.5	26.4	2.1
Gallbladder	--	--	--	--	16.0	1.3	13	1.8
Larynx	5.0	1.3	2.5	0.1	16.1	4	13.1	0.7
Liver	--	--	--	--	11.0	6.2	8.9	2.2
Lung	--	--	--	--	1.7	6.1	1.3	3.9
Oral cavity	9.1	8	4.6	2.7	32.4	28.5	27.3	15.8
Stomach	--	--	--	--	2.4	2.5	1.9	1.4
Female only								
Breast	--	--	1.3	8.4	--	--	5.3	33.5
Total		21.2		13.1		76.9		68.8

[a]EPC for a 10-year period, calculated using the number of cancers diagnosed among AN people for the 10-year period from 2006-2015.

Statistical methods

Prevalence estimates of cancer risk factors are given with 95% confidence intervals (CI), to account for the BRFSS sampling strategy and weighting. Differences in prevalence of cancer risk factors by sex and age categories (18-34, 35-49, 50-64, and 65+ years) were assumed to be statistically significant where 95% CI did not overlap.

Population attributable risk was estimated using Levin's formula:

$$PAR = [P_{pop} \times (RR-1)]/[P_{pop} \times (RR-1) +1]$$

where P_{pop} is the prevalence of the risk factor among Alaska Native people and RR is the relative risk of cancer associated with each risk factor (Levin, 1953). RR estimates specific to Alaska Native people were unavailable; therefore we used sex-specific estimates (where available), generated from meta analyses conducted among other US/European populations (Bagnardi et al., 2015; Botteri et al., 2008; Cheraghi et al., 2012; Friedenreich et al., 2010; Gandini et al., 2008; Jenabi and Poorolajal, 2015; Xue et al., 2017). Relative risk estimates used for calculations are given in Table 1. The estimated preventable cancers (EPC) for each risk factor was estimated by multiplying the PAR for that risk factor/cancer by the number of cancers at that site diagnosed among AN people over the most recent 10-year period: 2006-2015. A longer duration (i.e., 10-year period vs 5-year period examined for risk factor prevalence) was chosen to reduce the impact of case number fluctuations on our estimates of EPC, given small AN population numbers and case counts. Institutional Review Board Review and approval were not required for the current study because both BRFSS and SEER Program data are publically available, and all patient data were de-identified. Appropriate tribal review and approval was obtained for publication of this study.

RESULTS

Prevalence of modifiable cancer risk factors among Alaska Native People

Self-reported BRFSS prevalence of obesity, current smoking, physical inactivity, and current drinking (light/heavy/moderate) among AN people is given in Table 2. Over a third of AN people reported being obese; prevalence of obesity was higher among females (38.4%) than males (31.6%). Obesity prevalence was lowest in those aged 18-34 years, but was similar between all other age categories. Overall, smoking prevalence was almost 38%; current smoking was slightly higher among males (40.2%) than females (35.1%). Smoking prevalence was similar among those aged 18-34, 35-49, and 50-64; however, it was substantially lower among those aged 65 years and older. Overall, prevalence of physical inactivity was high, with over half (50.9%) of AN people reporting they did not meet the guidelines; this proportion was similar in strata of sex and age. Finally, over one third (42.4%) of AN people reported consuming at least one alcoholic drink/ month; a far smaller proportion reported moderate (8.9%) and heavy (10.45) drinking, respectively. The proportion of moderate and heavy drinkers was slightly higher among males, relative to females; yet there was no consistent pattern evident within strata of age.

Potentially preventable cancers among Alaska Native people

PAR and EPC for obesity-, smoking-, and physical inactivity-related cancers are given in Table 3. The number and proportion of potentially preventable cancers varied by risk factor and cancer site. The highest PAR was observed for smoking: over 70% of lung cancers (78.8% among males, 69.8% among females), and a similar proportion of laryngeal cancers (71.5% male, 67.7% female) could be potentially preventable with elimination of this risk factor. Overall, we estimated that approximately 800 cancers could be prevented in Alaska over a 10-year period if smoking were eliminated among AN people.

Obesity and physical inactivity represented a smaller, but still substantial, number of potentially preventable cancers (Table 3). Again, PAR varied by cancer site, but was highest for obesity and liver cancer (22.9% among males, 14.0% among females), and physical inactivity and lung cancer (17.5% among males, 18.1% among females). Both obesity and physical inactivity showed a particularly strong prevention potential for female cancers: PAR for endometrial cancer was 36.9% for obesity, and 18.1% for physical inactivity. Similarly, PAR associated with physical inactivity was 14.7% for breast cancer, and 10.9% for ovarian cancer. We estimated that approximately 210 cancers could be prevented among Alaska Native people by eliminating obesity and 317 by eliminating physical inactivity over a 10-year period.

Finally, we examined the prevention potential associated with both moderate and heavy drinking for alcohol-related cancers; these data are given in Table 4. Overall, both PAR and EPC were higher for heavy drinking than for moderate drinking; total EPC over a 10-year period for these risk factors was 146 and 34, respectively. As with the other risk factors that we examined, PAR varied by site. For heavy drinking, the highest PAR was observed for female breast cancer (33.5%), esophageal squamous cell carcinoma (31.4% males, 26.4% females), and cancers of the oral cavity (32.4% males, 27.3% females). In addition, a smaller, but still substantial proportion of cancers of the gallbladder, larynx and liver could also be prevented with the elimination of heavy drinking among AN people. Similar to heavy drinking, the highest PAR for moderate drinking was observed for esophageal squamous cell carcinoma (12.9% males, 6.7% females), and cancers of the oral cavity (9.1% males, 4.6% females). We estimated that eliminating moderate and heavy drinking may prevent up to 34 and 146 cancers among Alaska Native people, respectively, over a 10-year period.

DISCUSSION

The burden of cancer among AN people is high (Carmack, 2015; Kelly JJ et al., 2014). Yet, our results suggest that a potentially substantial proportion of these cancers may be prevented if exposure to four key modifiable risk factors: smoking, obesity, physical inactivity, and alcohol use, could be eliminated in this population. PAR was highest for several smoking-related cancer sites; the high prevalence of smoking among AN people and importance of tobacco cessation and prevention efforts has been previously recognized (Patten et al., 2007; Patten et al., 2008; Renner et al., 2004; Smith et al., 2010; State of Alaska Tobacco Prevention and Control Program, 2015; Wolsko et al., 2009). However, these results also suggest the importance of recognizing and addressing other modifiable risk factors in a comprehensive approach to the primary prevention of cancer. Such an approach is also likely to have additional benefit to AN people, as obesity, physical inactivity and alcohol use have been linked to other outcomes of concern, including diabetes, heart disease, chronic liver disease, and unintentional injury (Murphy et al., 1997; Murphy et al., 1995). While we recognize that reducing or eliminating exposure to these risk factors will provide a challenge to the Alaska Tribal Health System, this study provides data to help prioritize primary prevention efforts for the greatest reduction in AN cancer burden. These data reinforce the Alaska Tribal Health System's focus on tobacco use prevention and smoking cessation, and emphasize the importance of encouraging other healthy behaviors as well, including being physically active, maintaining a healthy weight, and low consumption of alcohol.

These data suggest that the greatest cancer prevention potential for the AN population is to reduce smoking. Of particular note, between 43%

and 79% of cancers of the lung, larynx, oral cavity, and bladder could be prevented with elimination of this risk factor. This is at the high end of the range of values observed across other, non-Native populations (Whiteman and Wilson, 2016), likely due to the high prevalence of smoking among AN people (Lanier et al., 2012; Redwood et al., 2010). In this study, prevalence of smoking was twice as high as has been reported for U.S. (2012) or Alaska whites (Alaska Department of Health and Social Services, 2016), and several rural Alaska boroughs (counties) with a high proportion of Alaska Native residents have among the highest smoking prevalence in the nation (e.g., 42% in the Northern Region, 2014 (Dwyer-Lindgren et al., 2014)). Furthermore in 2014, 15% of AN people reported using smokeless tobacco (Alaska Department of Health and Social Services, 2016), which has been linked to oral cancer, esophageal cancer, and pancreatic cancer, as well as heart and gum disease (Boffetta et al., 2008; Organization and Cancer, 2007). Our estimates of PAR did not include smokeless tobacco use; including this would likely inflate the estimates of PAR given here. Importantly, the high prevalence of smoking is likely a key contributor to several cancer disparities among AN people. For example, incidence of and mortality from lung cancer is 1.5 times higher among AN people, relative to U.S. whites (Carmack, 2015). Several state- and tribally-managed tobacco use prevention programs exist to encourage and support AN people who wish to quit smoking, including the Alaska Quitline and ANTHC's Tobacco Prevention and Control Program, which provides tobacco cessation services to AN people statewide, as well as training for community tobacco treatment specialists.

In addition to smoking, these data demonstrate that obesity and physical inactivity may also be associated with a substantial proportion of cancer among AN people (e.g., up to 37% for obesity and endometrial cancer); however, these results must be considered in context of what we know about obesity and physical activity among AN people. For example, the associations of obesity with chronic disease risk factors has been shown to be modified by intake of n-3 polyunsaturated fatty acids (Lemas et al., 2013; Makhoul et al., 2011; Vaughan et al., 2015), which are high in many AN traditional foods (Bersamin et al., 2008; Bersamin et al., 2006; Bersamin et al., 2007). Thus, it is possible that AN traditional subsistence activities, including consumption of AN traditional foods, may alleviate some of the cancer risk associated with obesity. Furthermore, AN people may experience physical activity differently than recommended by national guidelines, which could also modify the PAR estimates presented herein. Studies have shown that while few AN people may reach guideline amounts of moderate and vigorous physical activity, a potentially larger proportion may engage in lower intensity traditional activities such as harvesting wild berries and greens, and fishing for potentially longer periods of time (Redwood et al., 2009). An increasing body of literature supports the importance of increasing physical activity levels and avoiding sedentary behaviors (Arem et al., 2014; Arem et al., 2015; Howard et al., 2015; Matthews et al., 2012; Matthews et al., 2015; Moore et al., 2016), perhaps to include the AN (Yup'ik) concept of "keeping busy" (Hopkins et al., 2007), as a key component of disease risk reduction.

Several ANTHC programs support healthy behaviors around food and physical activity among Alaska Native people. Recently, ANTHC partnered with the State of Alaska's Play Every Day childhood obesity prevention campaign to create culturally-appropriate public service announcements for AN youth (Alaska Department of Health and Social (Services, 2017). In addition, ANTHC activities such as "Store Outside your Door" which promotes knowledge and use of AN traditional wild foods from around the state, and "Alaskan Plants as Foods and Medicine" promote healthy eating and traditional food consumption for all AN people. While these activities are not explicitly geared towards cancer prevention, our results suggest that reducing obesity and increasing physical activity may be beneficial in reducing cancer risk among AN people, and support the continued investment in, and evaluation of, such programs.

Alcohol use is also an important consideration for cancer prevention among AN people. These data demonstrate a lower prevalence of occasional drinking among AN people than has been reported for U.S. whites (Henley et al., 2014). Patterns of alcohol use may differ among AN people because of the cultural and political landscape around its consumption. Many rural AN communities are "dry" or "damp," meaning that they do not permit the consumption or sale of alcohol, respectively. We observed a high rate of abstinence among AN people, with over 65% of AN people reporting they do not currently drink (Table 2). Yet, our data also show that a substantial proportion of potentially preventable cancers may be related to alcohol use (e.g., up to 33.5% of breast cancers, among heavy drinking females). In addition to the substantial cancer prevention potential presented herein, elimination of excess alcohol use could have immediate implications for reducing other leading causes of AN mortality, including unintentional injury and suicide (Blake, 2016). While alcohol use is recognized as a cancer-causing agent (Baan et al., 2007), strategies and activities to reduce its use are not always included in tribal and state Comprehensive Cancer Control Plans (Henley et al., 2014), including the Alaska Tribal Health System Comprehensive Cancer Control Plan (2011-2017) (2006). Future iterations of the plan should include strategies that address the cancer prevention potential associated with reduced exposure to this risk factor at a population level.

Finally, these data can be compared to recent reports on PAR from across the U.S. A recent analysis by Islami and colleagues (Islami et al., 2017) estimated that up to 42% of incident cancers in the U.S. could be attributed to major modifiable cancer risk factors. As in the present study, smoking was a leading cause of both preventable cancers and cancer deaths: the authors estimated that approximately 80% of lung cancer cases were attributable to cigarette smoking. This is remarkably similar to our findings, given that prevalence of smoking and tobacco use is known to be substantially higher among Alaska Native people (e.g. 35-40% in the present study, versus approximately 15% nationwide (Jamal, 2016)). Nevertheless, differences can be observed: for example, approximately 20% of colon and rectal cancer cases (combined) among males may be attributed to obesity among AN men, compared to only 4.8% of colorectal cancer cases among U.S. males nationwide (Islami et al., 2017). Yet, despite differences in the methodology and cancer sites examined in the two studies, both estimate that a substantial proportion of cancers could be attributable to obesity, physical inactivity, and alcohol use. Similar findings have been reported for other populations globally (Arnold et al., 2015; Arriaga et al., 2017a; Parkin et al., 2011; Whiteman and Wilson, 2016). This growing body of research emphasizes need for dissemination and implementation of known cancer preventive measures. Our study further supports the need to understand population attributable risk associated with modifiable cancer risk factors in minority populations across the U.S., in order to be able to provide appropriate, population-specific prevention programs.

This is the first study to examine the burden of potentially preventable cancers among AN people using the population attributable risk metric, and provides a new way of looking at potential causes of cancer among this underserved population. Furthermore, these data may provide a novel and effective way of communicating risk to AN tribal health leaders and community members; future research should address the acceptability and accessibility of this metric for cancer risk communication among AN people. Yet this study also has several limitations that should be acknowledged. First, we were unable to use AN-specific relative risk estimates in our calculations; associations of risk factors with cancer outcomes may differ among AN people from the predominantly U.S./European populations on which the risk estimate meta-analyses used in this study were based. It is also assumed that risk factors for cancer among AN people mirror those observed in other populations; however, further research is necessary to explore whether there are AN specific risk or protective factors that might be the focus of successful primary prevention programs, and the strength of these associations. For example, the importance of *Helicobacter pylori* in the etiology of stomach cancer (Keck et al., 2014) and colorectal cancer (Lee et al., 2016; Qing et al., 2016; Sonnenberg and Genta, 2013; Zumkeller et al., 2006), or HBV/HCV in the etiology of liver cancer among AN people (Connelly et al., 2016) has been previously demonstrated. Furthermore, we acknowledge that our use of Levin's formula may have resulted in overestimation of the PAR, as this method does not account for effect modification, confounding, or competing risks (Arriaga et al., 2017b; Flegal, 2014; Flegal et al., 2004; Flegal et al., 2007). In particular, obesity and physical inactivity are likely to be highly interlinked. In addition, we note that PAR was calculated using BRFSS prevalence data from 2011-2015, and EPC using ANTR case count data from 2006-2015. Thus, our calculations do not account for any potential lag between exposure to the risk factors examined, and incidence of cancer. Changes in both risk factor prevalence, and cancer case counts, over time, would result in changes to the results presented herein. Finally, we note that BRFSS data are self-reported, and may not represent "true" risk factor exposure among the AN population. Importantly, potentially sensitive exposures such as alcohol may be underreported. Despite these limitations, these data provide a novel view of cancer among Alaska Native people, and provide data that may be useful to tribal health leaders and public health practitioners alike.

This study examined the population attributable risk for several leading modifiable risk factors for cancer among AN people. While smoking was the primary leading modifiable risk factor, a smaller, but still substantial proportion of cancers may be linked to other risk factors including obesity, physical inactivity and alcohol use. Our results demonstrate the need for a comprehensive approach to primary cancer prevention among AN people. Eliminating tobacco use, increasing healthy diet and physical activity, and moderating alcohol use would help substantially decrease the cancer burden and resultant health disparities experienced by AN people. By enhancing evidence-based prevention efforts in these areas, cancer morbidity and mortality would be reduced.

Acknowledgements

Dr. Nash and the Alaska Native Tumor Registry are supported by the NCI's Surveillance, Epidemiology and End Results Program, NCI contract number HHSN261201300010I, Task Order HHSN26100005. Dr. Redwood is supported by the Centers for Disease Control and Prevention, Building Public Health Infrastructure for Alaska Native People Component A, Grant # 1 NU58DP006379-01-00.

Conflict of interest statement

The author has declared that no competing or conflict of interests exists. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

SHN: conceptualization, formal analysis, methodology, project administration, writing - original draft, writing - review and editing. DGR: writing- review and editing.

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