ORIGINAL RESEARCH ARTICLE

Occurrence of pancreatic, biliary tract, and gallbladder cancers in Alaska Native people, 1973–2007

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***Objectives*:** To describe the occurrence of pancreatic, biliary tract, and gallbladder cancers within the Alaska Native (AN) population.
***Study design*:** Population-based analysis utilizing a tumor registry and comparative population data.
***Methods*:** Pancreaticobiliary cancers rates for AN people during 1973–2007 were determined from the Surveillance, Epidemiology, and End Results (SEER) AN Tumor Registry. Cancer incidence rates were age-adjusted to the World Standard Million and compared over 2 time periods with US white and black rates.
***Results*:** During 1973–2007, 213 AN people developed pancreatic cancer, 73 gallbladder cancer and 61 biliary tract cancer. Pancreatic cancer occurs at similar rates in AN men and women, but data for 1993–2007 indicate that the rates among AN men may be increasing. The incidence rate in AN women (9.5/100,000) was statistically higher than in US white women (5.8/100,000). The incidence for biliary tract cancer in AN men and gallbladder cancer in AN men and women is statistically higher than that for US whites and blacks.
***Conclusions*:** Pancreaticobiliary cancers, particularly biliary tract and gallbladder cancers, in both AN men and women and pancreatic cancer in women occur at an increased rate in AN people. Risk factors relating to the elevated rate are discussed. Certain factors are potentially modifiable, such as the use of tobacco and obesity.

Keywords: *Alaska Native*; *American Indian*; *pancreatic cancer*; *biliary tract cancer*; *gallbladder cancer*; *epidemiology.*

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Pancreaticobiliary cancers vary significantly in their occurrence and mortality rates worldwide (1,2). Pancreaticobiliary cancers are uncommon cancers in the general US population. In the USA, pancreatic cancer accounts for 2.6% of all new cancer diagnoses, while the occurrence of biliary tract and gallbladder cancers account for 2.1% of all new cancer diagnoses (3). The true number of biliary tract cancers has been more difficult to obtain, as intrahepatic biliary cancers are generally combined with hepatocellular carcinoma for reporting purposes. While pancreaticobiliary cancers account for only 4–5% of all cancers, they tend to be aggressive cancers with a high mortality rate, accounting for nearly 6% of all cancer-related deaths. Only limited information is available in regard to the incidence and etiology of this group of cancers, particularly at the level of specific ethnic or racial groups.

More detailed information has been published on the incidence of pancreatic cancer. Based on data from the Surveillance, Epidemiology, and End Results (SEER) program, the incidence of pancreatic cancer in US men significantly decreased from 1973 to 2002, while in women it increased until 1984 and has since slowly declined (4). In the USA, pancreatic cancer occurs more commonly in men, with an incidence that is nearly 30% higher than in women (5). The highest rates of pancreatic cancer are noted in blacks, followed by whites and Hispanics. Lower rates are noted for Asians/Pacific Islanders and all American Indians (AI)/Alaska Native (AN) people combined (6). More than 90% of cancers of the pancreas are adenocarcinomas. Less frequent cancers include islet cell cancers, intraductal neoplasms and cystic neoplasms.

While the incidence of biliary tract and gallbladder cancers in other populations has been described in

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detail, the incidence in Indigenous populations of North America is not well described. For the entire US population, a comparison of the incidence for 2 different time periods in the USA has shown that the age-adjusted incidence rates of intrahepatic cholangiocarcinoma increased by 165% from 0.32 per 100,000 in the time period 1975 to 1979 to 0.85 per 100,000 in 1995 to 1999, whereas extrahepatic cholangiocarcinoma declined by 14% (7). For cancers of the gallbladder and extrahepatic cholangiocarcinoma, the highest rates are among Hispanics, AI/AN and Asian-Pacific Islanders. Asian-Pacific Islanders and Hispanics of both sexes had the highest incidence of extrahepatic cholangiocarcinoma compared to white men and women who have a significantly lower incidence of gallbladder cancer (8).

Alaska Native (AN) people represent an Indigenous population within Alaska, as described in detail elsewhere (9). The occurrence of cancer and associated trends, for cancer overall and selected sites, in this population have been well described in multiple prior publications, including a 35-year summary (10). With the intent to more clearly define the incidence of pancreaticobiliary tumors, this review reports the incidence of this group of cancers in the AN population for the 35-year period of 1973–2007. The availability of such information will provide a better understanding of the occurrence of these cancers and therefore potentially an opportunity to identify the risk factors for their development. Ultimately this may allow for focused intervention in high-risk groups for both prevention and early detection.

Material and methods

Study population

AI/AN represent a diverse group of people indigenous to North America. The US Census Bureau estimates that in the year 2000 there were 2,402,000 AI/AN from over 500 tribes in the USA (11). In 2000, ca. 119,000 AN people resided in Alaska and represent 3 major ethnic groups that include Eskimo, Aleut and Alaska Indian people. Eskimos comprise 52% of the Native population and include 2 major language groups, the Yupik Eskimo of southwestern Alaska and Inupiaq (Inuit) of northern Alaska (12,13). The Inupiaq share the same language with the Inuit of Canada and Greenland. Alaska Indian people, 36% of the Native population, include groups from the Athabaskan tribes residing in the interior portion of Alaska and Tlingit, Haida and Tsimshian tribes of southeastern Alaska. The Aleut comprise 12% of the population and have traditionally resided on the Aleutian Islands and the Alaska Peninsula.

Source of data

The National Cancer Institute's SEER Program registry, the Alaska Native Tumor Registry (ANTR), a population-based registry, was used to identify all cases of pancreaticobiliary cancer occurring during the 35-year time period 1973–2007. The registry provides a summary of all invasive cancers occurring in the AN population since 1969. Classification of ethnicity is based on self-reporting at the time of hospital/clinic registration. Cases included in the registry are identified through a variety of sources including: (a) hospital discharge diagnoses for all tribal health facilities in the state; (b) tumor registry and pathology files of the Alaska Native Medical Cancer; (c) other in-state hospital tumor registries, pathology and autopsy reports; (d) the Alaska and Washington state cancer registries; and (e) death certificates for AN people. Prior to 1984, the registry collected data on patient demographics, primary cancer site, histology and basis of confirmation of the diagnosis. Since 1984, more detailed information has been collected including cancer staging, treatment and follow-up. Procedures for data collection and coding follow those of the SEER Program. Changes over time in cancer staging rules did not allow for grouping recent data with earlier reports. Pancreas only was staged for the period 2004–2007, based on collaborative stage coding and presented as SEER Historic Stage A categories: local, regional and distant.

Population estimates of AN people are based on 1970, 1980, 1990 Census population counts, and from the National Center for Health Statistics bridged census 2000 population estimate for AN people. We computed cancer incidence rates from malignant cases, age adjusted to the WorldStandard Million and expressed as per 100,000 population for a 35-year period 1973–2007, a recent 15-year period 1993–2007 and an earlier 20-year period 1973–1992. Cancer rates shown for other US populations are from SEER*Stat, a limited-use research dataset available online from the National Cancer Institute, Surveillance, Epidemiology and End Results (SEER) Program. 95% confidence intervals for age-adjusted rate comparisons were calculated using Tiwari method. Five-year relative survival rates for pancreas and gallbladder sites were calculated by the actuarial method using SEER* Stat software. Survival rates for biliary cancers were not calculated due to small case numbers. Alaska Native expected survival tables based on 1991–2005 Alaska Native mortality rates for individual years; US expected survival table for individual years 1970–2000.

Patients with pancreaticobiliary cancers coded by the International Classification of Diseases for Oncology (ICD-O-3) system as arising from the pancreas (C25.x), gallbladder (C23.9), or biliary tract (C22.1, C22.x) were selected for inclusion in this study.

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Results

Overall

During the 35-year period of review (1973–2007) a total of 347 AN people were diagnosed with pancreaticobiliary cancer. The distribution of these by anatomic site and histology is summarised in Table I. Overall, 213 AN people had pancreatic cancer, 73 had gallbladder cancer and 61 had a biliary tract cancer. A histologic or cytologic diagnosis was made in 82% of patients. The proportion of patients with pancreatic cancer having a histiologic or cytologic diagnosis was lower (72%) than for patients with either biliary tract (87%) or gallbladder cancer (98%).

Pancreatic cancer

The histologic classification of the 213 patients with pancreatic cancer is shown in Table I. Overall, 38 (18%) had carcinoma, 125 (58%) had adenocarcinoma, while 13 had a mucin producing, serous or cystic carcinoma. Islet cells carcinomas were uncommon, with only 2 having been diagnosed. US whites showed similar histologic distribution.

The incidence of pancreatic cancer (Table II) is higher in US men compared to women, but not among AN where 35-year rates for men and women are similar. AN women have higher rates compared to US white women, but similar to those seen in US black women. AN men have rates similar to US white but lower than US black men. The incidence for women of all race groups remained stable over the 2 time periods compared. The incidence for AN men increased more than 50% to a rate similar to that seen in US black men. The age-specific rates (Table III) are similar to US whites and blacks of the same age groups. Staging was assessed for the time period 2004–2007. During this time period 5% of patients

Table I. Summary of pancreatobiliary cancers among Alaska Native People (n = 347), Compared to US Whites, 1973–2007[a]

	Pancreatic cancer (n = 213)	Biliary tract cancer (n = 61)	Gallbladder cancer (n = 73)
Number of cases (n = 347)			
Male	102	38	26
Female	111	23	47
Total	213	61	73
Age (years)			
Median (Range)	66 (32–89)	66.5 (38–91)	70 (33–90)
Ethnicity (%AN population)	%	%	%
Eskimo (52%)	52	57	42
Indian (36%)	32	31	54
Aleut (12%)	16	11	4
Histology (WHO ICD-O (3rd))	ANUSW (%)	ANUSW (%)	ANUSW (%)
8000–8009 unspecified neoplasm	15 7	23	32
8010–8049 epithelial neoplasm	18 26	7 10	89
8140–8389 adenocarcinomas	58 57	86 81	7978
8440–8499 cystic, mucinous, serous	6 5	3 4	76
8500–8549 ductal and lobular	3 4	0 1	00
8560–8579 complex epithelial	0 0	0 0	33
Other	0 1	2 1	03
Biliary tract sub-sites		ANUSW (%)	
Intrahepatic		20 25	
Extrahepatic (subgroups)		80 75	
(Extrahepatic bile duct)		*(43)(25)*	
(Ampulla of Vater)		*(37)(57)*	
(Overlapping/biliary, NOS)		*(20)(18)*	
Stage (2004–2007)	ANUSW (%)		
Localised	59		
Regional	2427		
Distant	6151		
Unstaged	1014		

[a]Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-Seer 17 RegsLimited-Use + Hurricane Katrina Impacted Louidiana Cases, November 2009 Sub (1973–2007 varying), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, released April 2010, based on the November 2008 submission.

Table II. Age-adjusted (World Standard Million) incidence (95% confidence intervals) rates per 100,000 of pancreaticobiliary cancers by time-period and gender, 1973–2007

Time period	Alaska Native	US white	US black
Men			
Pancreatic cancer			
1973–2007	9.4 (7.7–11.4)	8.1 (8.0–8.2)	12.2 (11.8–12.6)
1973–1992	7.7 (5.4–10.7)	8.3 (8.2–8.4)	12.9 (12.3–13.4)
1993–2007	10.7[a] (8.3–13.7)	7.9 (7.8–8.1)	11.6 (11.2–12.1)
Biliary cancer			
1973–2007	3.4[a,b] (2.4–4.7)	1.5 (1.4–1.5)	1.2 (1.1–1.4)
1973–1992	3.5[a,b] (2.0–5.7)	1.3 (1.2–1.3)	1.1 (0.9–1.2)
1993–2007	3.4[a,b] (2.1–5.1)	1.6 (1.6–1.7)	1.4 (1.3–1.6)
Gallbladder cancer			
1973–2007	2.4[a,b] (1.6–3.6)	0.5 (0.5–0.5)	0.6 (0.5–0.7)
1973–1992	2.5[a,b] (1.2–4.4)	0.6 (0.5–0.6)	0.6 (0.5–0.7)
1993–2007	2.4[a,b] (1.3–4.0)	0.4 (0.4–0.5)	0.6 (0.5–0.7)
Women			
Pancreatic cancer			
1973–2007	9.5[a] (7.7–11.4)	5.8 (5.7–5.9)	9.1 (8.9–9.4)
1973–1992	10.2[a] (7.4–13.5)	5.8 (5.7–5.9)	9.3 (8.9–9.7)
1993–2007	9.0[a](6.9–11.5)	5.8 (5.7–5.9)	9.0 (8.6–9.3)
Biliary cancer			
1973–2007	1.9[a,b] (1.2v2.8)	1.0 (0.9–1.0)	0.8 (0.7–0.9)
1973–1992	0.9 (0.3–2.2)	0.9 (0.8–0.9)	0.7 (0.6–0.8)
1993–2007	2.5[a,b] (1.5–4.0)	1.1 (1.0–1.1)	0.9 (0.8–1.0)
Gallbladder cancer			
1973–2007	3.9[a,b] (2.9–5.2)	1.0 (0.9–1.0)	0.9 (0.9–1.0)
1973–1992	6.2[a,b] (4.1–8.8)	1.1 (1.1–1.2)	0.8 (0.7–1.0)
1993–2007	2.3[a,b] (1.3–3.8)	0.8 (0.8–0.8)	1.0 (0.9–1.2)
Men and women combined			
Pancreatic cancer			
1973–2007	9.4[a] (8.2–10.8)	6.9 (6.8–6.9)	10.5 (10.3–10.7)
1973–1992	8.9[a] (7.1–11.1)	6.9 (6.8–7.0)	10.9 (10.5–11.2)
1993–2007	9.7[a] (8.1–11.6)	6.8 (6.7–6.9)	10.2 (9.9–10.5)
Biliary cancer			
1973–2007	2.6[a,b] (2.0–3.4)	1.2 (1.2–1.2)	1.0 (0.9–1.1)
1973–1992	2.2[a,b] (1.3–3.3)	1.1 (1.0–1.1)	0.9 (0.8–0.9)
1993–2007	2.9[a,b] (2.0–4.0)	1.3 (1.3–1.3)	1.1 (1.0–1.2)
Gallbladder cancer			
	3.2[a,b] (2.5–4.0)	0.8 (0.7–0.8)	0.8 (0.7–0.8)
1973–1992	4.4[a,b] (3.1–5.9)	0.9 (0.9–0.9)	0.7 (0.7–0.8)
1993–2007	2.3[a,b] (1.6–3.3)	0.6 (0.6–0.7)	0.8 (0.8–0.9)

[a]AN incidence rate > US white rate; $p < 0.05$.
[b]AN incidence rate > US black rate; $p < 0.05$.

with pancreatic cancer had disease staged as local, 24% as regional and 61% as metastatic (Table I). The remaining 10% had no staging information available.

Few patients with pancreatic cancer received therapy. For the time period 1984–2008, 5% underwent surgery, 18% received chemotherapy and 7% received radiation. Comparison of 5-year relative survival rates showed no statistically significant differences between AN people and US whites.

Biliary tract cancer

The distribution of biliary tract cancers by anatomic site is shown in Table I. Intrahepatic cholangiocarcinoma accounted for 20% of all biliary tract cancers. Of the 48

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Table III. Age-specific incidence (95% CI) rates per 100,000 of pancreaticobiliary cancers by age group and gender, 1973–2007

Age group	Alaska Native	US white	US black
Men			
Pancreatic cancer			
30–39	1.5 (0.3–4.2)	0.8 (0.7–0.8)	1.5 (1.2–1.8)
40–49	8.2 (4.3–14.0)	4.5 (4.3–4.7)	7.1 (6.4–7.8)
50–59	18.6 (11.4–28.7)	16.3 (15.9–16.8)	28.8 (27.1–30.7)
60–69	46.7 (31.5–66.7)	40.6 (39.8–41.4)	63.7 (60.4–67.1)
70 +	83.1 (58.0–115.4)	79.1 (78.0–80.4)	102.4 (97.4–107.6)
Biliary cancer			
30–39	–	0.2 (0.2–0.2)	0.1 (0.1–0.2)
40–49	–	0.8 (0.7–0.9)	0.9 (0.7–1.3)
50–59	5.6 (2.0–12.1)	2.5 (2.4–2.7)	2.8 (2.3–3.4)
60–69	19.0[a,b] (9.8–33.1)	6.6 (6.3–7.0)	5.5 (4.5–6.5)
70 +	38.5[a,b] (22.3–62.1)	15.8 (15.3–16.3)	12.1 (10.4–13.9)
Gallbladder cancer			
30–39	–	0.0 (0.0–0.1)	0.1 (0.0–0.2)
40–49	–	0.2 (0.2–0.2)	0.3 (0.2–0.5)
50–59	1.9 (0.2–6.7)	0.7 (0.7–0.8)	1.0 (0.7–1.4)
60–69	10.9[a,b] (4.4–22.4)	2.3 (2.1–2.5)	2.3 (1.7–3.0)
70 +	37.3[a,b] (21.2–60.8)	6.4 (6.0–6.7)	6.8 (5.5–8.2)
Women			
Pancreatic cancer			
30–39	1.4 (0.3–4.0)	0.5 (0.5–0.6)	0.9 (0.7–1.1)
40–49	6.9[a] (3.4–12.3)	2.8 (2.6–2.9)	5.2 (4.7–5.8)
50–59	20.0[a] (12.6–30.3)	10.6 (10.3–11.0)	18.0 (16.7–19.3)
60–69	45.1[a] (30.5–64.4)	28.0 (27.4–28.7)	46.2 (43.7–48.8)
70 +	87.6[a] (63.3–117.8)	61.2 (60.3–62.1)	88.0 (84.4–91.7)
Biliary cancer			
30–39	–	0.1 (0.1–0.2)	0.2 (0.1–0.3)
40–49	–	0.5 (0.5–0.6)	0.4 (0.2–0.6)
50–59	6.4[a,b] (2.6–13.1)	1.7 (1.6–1.8)	1.7 (1.3–2.1)
60–69	4.6 (0.9–13.4)	4.4 (4.1–4.6)	3.8 (3.1–4.5)
70 +	19.3 (9.1–35.6)	10.4 (10.0–10.7)	8.0 (7.0–9.1)
Gallbladder cancer			
30–39	–	0.1 (0.1–0.1)	0.1 (0.0–0.2)
40–49	–	0.4 (0.4–0.5)	0.7 (0.5–1.0)
50–59	8.2[a,b] (3.7–15.5)	1.7 (1.5–1.8)	2.1 (1.7–2.6)
60–69	22.2[a,b] (12.4–36.6)	4.6 (4.3–4.8)	4.1 (3.4–5.0)
70 +	37.8[a,b] (23.2–58.1)	10.9 (10.6–11.3)	8.9 (7.8–10.1)
Men and women combined			
Pancreatic cancer			
30–39	1.4 (0.5–3.1)	0.6 (0.6–0.7)	1.2 (1.0–1.3)
40–49	7.5[a] (4.8–11.2)	3.6 (3.5–3.8)	6.1 (5.6–6.6)
50–59	19.3[a] (13.9–26.1)	13.4 (13.2–13.7)	23.0 (21.9–24.1)
60–69	45.9[a] (35.0–59.1)	34.0 (33.5–34.5)	53.9 (51.9–56.0)
70 +	85.1 (67.3–106.2)	68.4 (67.7–69.1)	93.6 (90.7–96.6)
Biliary cancer			
30–39	–	0.2 (0.1–0.2)	0.2 (0.1–0.2)
40–49	0.9 (0.2–2.7)	0.7 (0.6–0.7)	0.6 (0.5–0.8)
50–59	6.0[a,b] (3.2–10.2)	2.1 (2.0–2.2)	2.2 (1.9–2.5)
60–69	11.6[a,b] (6.5–19.2)	5.4 (5.2–5.6)	4.5 (3.9–5.1)
70 +	27.6[a,b] (18.1–40.4)	12.4 (12.1–12.7)	9.6 (8.7–10.5)

Table III (*Continued*)

Age group	Alaska Native	US white	US black
Gallbladder cancer			
30–39	–	0.1 (0.0–0.1)	0.1 (0.1–0.2)
40–49	–	0.3 (0.3–0.3)	0.6 (0.4–0.7)
50–59	5.1[a,b] (2.5–9.0)	1.2 (1.1–1.3)	1.6 (1.3–1.9)
60–69	16.7[a,b] (10.4–25.2)	3.5 (3.3–3.7)	3.3 (2.8–3.9)
70 +	37.3[a,b] (26.1–51.6)	9.1 (8.9–9.4)	8.2 (7.3–9.1)

[a]AN age-specific rate > US white rate; $p < 0.05$.
[b]AN age-specific rate > US black rate; $p < 0.05$.

extrahepatic biliary tract cancers, 17 (35%) were in the ampulla of Vater. The incidence of biliary tract cancers (intrahepatic and extrahepatic) occurs at a rate higher than that seen in other US ethnic/racial groups (Table II). Overall incidence is higher among men than in women for all groups. While the number of patients developing a biliary tract cancer has been small, the incidence for AN men appears to be stable while an increase has occurred in women. The age-specific rates suggest that biliary cancers may occur at a somewhat older age in AN people compared to other US groups. AN men aged 60 and older have the highest incidence rates compared to all other men and women of the same ages.

Sixteen percent of patients with biliary tract cancers underwent surgery, while 9% received chemotherapy and 9% received radiation. Survival rates appeared similar to US white rates.

Gallbladder cancer

The incidence of gallbladder cancer for both AN men and women (Table II) occurs at a higher rate than that seen in US whites or blacks. However, a decrease in the incidence in AN women occurred in the most recent time period reviewed. Decreases in gallbladder incidence rates occurred among US whites but not among US blacks. Age-specific rates (Table III) indicate that gallbladder cancer occurs at higher rates in AN people aged 50 and older, particularly women, compared to other racial groups.

Fifteen of the patients (31%) underwent surgery, while 10% received chemotherapy, 8% received radiation. Survival rates are not statistically different from the US rates overall.

Discussion

Outside of gallbladder cancer very little has been described about the occurrence of pancreaticobiliary cancers among AN people. In 2 prior general reviews of cancer in the Inuit people of Alaska, Canada and Greenland, the incidence of pancreatic cancer was noted to be higher for Inuit people, particularly from Alaska and Greenland, compared to the standard world population rate and US white rate (14,15). However, overall rates did not appear to deviate significantly from international rates. In separate reviews, the incidence of pancreatic cancer in the Sami of Scandinavia appears similar to that seen in other non-Sami populations (16,17). Within the general US population, some variation in the incidence of pancreatic cancer is seen by region and ethnic/racial group. In a review of 3 decades of data from 9 different SEER registries in the USA, an overall decline in the incidence of pancreatic cancer was seen, most pronounced in men (4).

As reviewed elsewhere, during the period 1999–2004 the incidence of pancreatic cancer for all AI/AN people combined was observed to be significantly lower than that observed in non-Hispanic Whites (18). However, significant variations were noted by region, with the highest incidence seen in AN men and in AI women from the Northern Plains. The current review of the 35-year period 1973–2007 for AN people reveals that the incidence of pancreatic cancer increased for men while remaining stable for women during the 2 time periods assessed. The current incidence of pancreatic cancer in AN people is higher than that observed in US whites and similar to that observed in US blacks. Pancreatic cancer mortality rates in AN people for 1990–2006 are also similar to US blacks, and both AN and black rates are higher than US whites. There were no changes in the pancreatic mortality rates in AN people over 2 periods, 1990–1999 and 2000–2006. The less common forms of pancreatic cancer, such as islet cell tumors, appear to occur in AN people at a rate similar to that reported for other populations (19).

The distribution of pancreatic cancer by stage for AN people is similar to that observed in the general US population as reported by the SEER Program. The age-specific rates also indicate that the age at which pancreatic cancer occurs is similar to that seen in the general US population, although marked variations exist in the actual rates (Table III). The reason for the higher rates of pancreatic cancer among AN people and the apparent

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increase in men is not entirely clear. A variety of risk factors for pancreatic cancer have been described, including smoking, obesity and diabetes (20). Tobacco use, including cigarettes, pipe tobacco and spit tobacco, is one of the more prominent risk factors identified to date with an attributable risk from smoking at ca. 25% (21–23). Rates of tobacco use are higher in AN people. In 2 recent Behavioral Risk Factor Surveillance System (BRFSS) surveys, for years 2006 to 2009, indicate the rate of smoking in AN people is between 39 and 45% compared to 18–19% in non-Native Alaskans (24). With cessation of tobacco use the risk for pancreatic cancer has been observed to progressively diminish (22).

Obesity has also been reported as a risk factor for pancreatic cancer, including several meta-analyses (25,26). It remains unclear if there is a direct association between obesity and the risk of pancreatic cancer or if it is reflecting other risk factors such as diet and physical inactivity. The manner in which weight is gained may also modify the risk of pancreatic cancer. Central obesity has been associated with a higher rate of insulin resistance, potentially explaining a link noted with diabetes and pancreatic cancer (27,28). In the Alaskan BRFSS 2008 survey, the rate of obesity (body mass index 30 +) was 37% forAN people compared to 26% in non-Native Alaskans. In addition, AN people tend to have higher rates of central obesity (29).

The relation between diabetes and pancreatic cancer is complex. While several studies have shown an increased rate related to type 2 diabetes, there is also some evidence to suggest that diabetes may occur in parallel with the development of pancreatic cancer. With long-standing type 2 diabetes, the risk of pancreatic cancer is increased by up to 50% (30,31). With treatment of diabetes, at least with the drug metformin, the risk of pancreatic cancer appears to diminish (32). Several studies have also shown that a high proportion of patients with pancreatic cancer have new onset diabetes that may resolve with resection of the cancer (31,33). The rate of diabetes in AN people is increasing and now occurs at the same level as seen in non-Natives. Current published reports indicate that ca. 4% of AN people have diabetes (34,35). The potential association between diabetes and pancreatic cancer in AN people has not yet been studied.

The historical incidence of biliary tract cancers in general has been less well described, in part due to the inclusion of intrahepatic biliary cancers with other liver cancers in most published reports. In a published review of the incidence of biliary tract cancers from around the world it was noted that the incidence of extrahepatic bile duct cancer is generally low except in Japan and Korea, particularly in men (36). In the USA there is evidence to indicate that the incidence of cholangiocarcinoma is increasing, particularly intrahepatic cholangiocarcinoma (7). The combined incidence of gallbladder and biliary tract cancers in the Circumpolar Inuit is among some of the highest rates in the world (15,16). Similar high rates are not observed in the Sami (17,18). Within AN people the incidence of biliary tract cancers appears to occur at a rate higher than that occurring in US whites and blacks. While the number of actual cases is small, there is a suggestion of some increase in the incidence in AN women. Little is known about the incidence of biliary tract cancers in other AI groups in the USA. In comparison to other Indigenous populations in circumpolar regions for the time period 1989–2003 the incidence of biliary tract and gallbladder cancers combined among AN Eskimos was higher than that reported for Eskimo (Inuit) from either Canada or Greenland (15,37).

The underlying risk factors for biliary tract cancers are not well defined. Conditions leading to the development of chronic inflammation in the biliary tract have been associated with the development of cholangiocarcinoma. These conditions include primary sclerosing cholangitis (PSC), hepatolithiasis, parasitic infections, chronic typhoid carriage, bile duct adenoma, biliary papillomatosis and certain drug exposure (38). PSC is one of the most common causes of cholangiocarcinoma in the Western world. However, in prior reviews of chronic inflammatory liver disease in AN people no documented cases of PSC were found (39,40).

Several studies have shown an association between viral hepatitis and cholangiocarcinoma. In a large case–control study in Korean patients, a significant association was seen with seropositivity for hepatitis B, but not hepatitis C, and intrahepatic cholangiocarcinoma (41). In a separate study involving US Veterans, a significant association was seen with hepatitis C and a risk of intrahepatic cholangiocarcinoma (42). In both studies, heavy alcohol use also contributed to the increased risk. Similar findings have been noted between hepatitis C and alcoholic cirrhosis and the development of the precursor lesion biliary intraepithelial neoplasia. Using explanted livers from patients with alcoholic cirrhosis, hepatitis C-related cirrhosis, a combination of both or neither, both alcohol and hepatitis C were associated with a higher risk of biliary intraepithelial neoplasia (43). While hepatitis C exists within the AN population, its prevalence is not well defined (44). Both hepatitis C and alcohol are important contributors to chronic liver disease in AN people, although it is unclear what role they may have in the development of cholangiocarcinoma (39).

The incidence of gallbladder cancer varies markedly in different regions of the world (36). Some of the highest rates are seen in Indigenous populations of both North and South America (45). In selected Indigenous populations from other parts of the world, rates of gallbladder cancer are also high compared to the non-Indigenous groups. New Zealand Maori have a relatively high

incidence of gallbladder cancer, and the incidence is equal in both Maori men and women, while cancers of the extra-hepatic bile duct and ampulla of Vater are rare in Maori. In contrast cancers of the gallbladder, extrahepatic bile ducts and ampulla are rare in Pacific Islanders (46).

Within AI and AN people the incidence of gallbladder cancer occurs at a rate higher than that seen in other groups. AN people and AI people from the south-west USA have the highest rates among all AI and AN people (47). Within the AN population, Alaska Indians have the highest proportion of gallbladder cancer (Table I), with 54% of gallbladder cancers occurringin this group, while AI people represent only 36% of the total AN population. Interestingly, the rate of gallbladder cancer in AN women appears to have recently decreased. In addition, it appears that there may be a higher proportion of patients with regional rather than distant disease in AN people compared to US whites. This may in turn be the underlying reason that despite a high incidence of gallbladder cancer the mortality rate from gallbladder cancer among AN people is only slightly above that seen in the general US population (48).

Gallstones are one of the predominant risk factors for gallbladder cancer. It has been long recognised that Native people of both North and South America have a higher rate of gallstone formation (49,50). Several studies have concluded that this higher rate is related to a genetic component predisposing to cholesterol gallstone disease (50). The occurrence of gallbladder disease was recently assessed in defined AI populations in the Strong Heart study (51). The Strong Heart study involved a longitudinal assessment of cardiovascular disease and its risk factors among members aged 45 years and older of 13 Indian tribes and communities, but did not include Alaska. As a substudy assessing gallbladder disease, a multivariate logistic regression analysis was performed, which showed that age, AI heritage and waist circumference were associated with gallbladder disease among men; and age, AI heritage, diabetes and parity were associated with gallbladder disease among women. Body mass index was not independently associated with gallbladder disease in either sex.

Given the strong association between gallstones and gallbladder cancer, several studies have looked at the impact of cholecystectomies in potentially reducing the rate of gallbladder cancer. Studies from both Chile and Scotland have shown an apparent association between the rates of cholecystectomies and the incidence of gallbladder cancer (49,52). Any potential impact of cholecystectomies in AN people on the incidence of gallbladder cancer is yet to be explored.

In summary, pancreaticobiliary cancers, particularly biliary tract and gallbladder cancers, occur at an increased rate in AN people. With a recognition of the increased rate and potential risk factors related to these cancers it may be possible to develop specific interventions for those factors that are potentially modifiable. With a growing number of treatment options for patients with pancreaticobiliary cancers it may also be possible to enhance the care of patients with these forms of cancers.

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