AMERICAN INDIAN CULTURE AND RESEARCH JOURNAL 16:3 (1992) 77–86

Gallstones and Gallbladder Cancer in Southwestern Native Americans

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ABSTRACT

We have studied the relationship between gallstones and gallbladder cancer in American Indians located in the southwestern United States. As determined in a case-control study, the overall age- and sex-adjusted relative risk for this group was 20.9 (95 percent confidence interval 8.1–54). The corresponding relative risk for non-Indian subjects was significantly less: 4.4 (95 percent confidence interval 2.6–7.3). Indian subjects were more likely to have stones $\geq$cm than non-Indian subjects: Age-adjusted odds ratio = 1.5, 95 percent confidence interval 1.2–2.00. Large stones appear to be associated with an increased risk of gallbladder cancer, perhaps because they have been present longer than small stones.

Many other Native American populations in the Western Hemisphere ranging from Alaska to South America are also prone to gallbladder cancer. These widely separated groups may share a common genetic factor leading first to obesity and then to gallstones and gallbladder cancer.

INTRODUCTION

In most world populations, gallbladder cancer is an exceptionally

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rare tumor, often discovered unexpectedly at the time of cholecystectomy and nearly always incurable. Thus, it is surprising that this unusual tumor should be so frequent in Native Americans—a population where the overall risk of cancer is low. Populations with a preponderance of American Indians and with excessive incidence and/or mortality rates from gallbladder cancer are widely distributed throughout the Western Hemisphere from Alaska to South America [1,2]. Since these populations are dispersed over such a wide geographic area, it would seem unlikely that the increased frequency of this tumor is related to a single environmental factor such as diet. An alternative explanation based on genetics has been proposed to explain the high risk in Native Americans [3,4]. The hypothesis is as follows: Native American populations are believed to have reached the Western Hemisphere during the last glacial epoch, approximately 10,000-24,000 years B.P., via a land bridge across the Bering Straits. The survivors of this arduous crossing would have been exposed to the harsh climate of that period, and the ability to rapidly store excess calories as body fat would have been advantageous; over many generations, genetic drift might have led to the development of the so-called thrifty gene [5]. Persistence of this trait when climatic stresses no longer exist would now be disadvantageous, because it might lead to obesity, gallstones, and diabetes. Gallstones, in turn, have been thought to be associated with gallbladder cancer.

Thus one explanation for the high risk of gallbladder cancer in Native Americans might be that it is linked to the well-known high prevalence of gallstone disease in this group [6]. To explore the relationship between gallstones and gallbladder cancer, we have conducted epidemiologic studies in Native Americans of the southwestern United States.

METHODS

We first conducted a case-control study of gallbladder cancer (ICD 156.0) in three racial groups: 57 American Indians treated at the Phoenix Indian Medical Center, Arizona; 37 Black subjects from Charity Hospital, New Orleans, Louisiana; and 37 white subjects from Malmo, Sweden [7]. These 131 subjects with gallbladder cancer were matched by age, sex, and race with a total of 2,399 subjects without gallbladder cancer where autopsies had been performed. Control subjects were excluded if the gallbladder had previously been removed, if gallstones were listed as a cause of death, or if appropriate information about the gallbladder was missing. The final control group consisted of 84 percent of the initial sample.

The relative risk as approximated by the odds ratio was used to measure the association between gallstones and gallbladder cancer. These estimates of the relative risk were then used to calculate the twenty-year cumulative risk of gallbladder cancer in subjects with gallstones.

After completion of this study, we carried out another project aimed at investigating the rate of growth of gallstones in native and nonnative American females, distribution of stones by size, and the relationship between size of the largest gallstone and gallbladder cancer [8]. For these studies, we relied on measurement of the largest gallstone encountered in 965 subjects undergoing cholecystectomy for nonmalignant disease at the Phoenix Indian Medical Center, Arizona, and 528 Black subjects and 168 white subjects operated on for nonmalignant gallbladder disease at Charity Hospital, New Orleans, Louisiana. During this same period, fifteen subjects (eleven Indian, four non-Indian) were identified with malignant gallbladder disease and with accurate measurements of the size of the largest gallstone detected at surgery. This study was therefore based on 1,676 females at the two study centers, with information about stone size from 87 percent of all subjects operated on for either benign or malignant gallbladder disease during a seven-year period.

RESULTS

Gallstones and the Risk of Gallbladder Cancer

Table 1 contains basic epidemiologic data obtained during this study. In all racial groups, gallbladder cancer was more frequent in females than males, and there appeared to be a consistently strong relationship between gallstones and gallbladder cancer. For non-Indian subjects, the overall Mantel-Haenszel RR was 4.4 (95 percent confidence limits 2.6–7.3). No significant differences were apparent between whites and Blacks or between males and females. For Native Americans, the overall age- and sex-adjusted relative risk was significantly higher: RR = 20.9, 95 percent CI = 8.1–54 (table 2).

TABLE 1
Characteristics of Gallbladder Cancer Cases and Controls*

Race and Sex	Cases: No. (%) with Stones	Cases: Mean Age, Yr. ± SD	Cases: Gallbladder Cancer Incidence/100,000/yr**	Controls: No.	Controls: Percent with Stones* (95% Confidence Limits)	Controls: Mean Age, Yr ± SD
Black male	14 (43)	68.1±10.5	2.3	63	12 (6–24)	67.5±9.2
Black female	23 (60)	72.5±9.4	3.0	121	19 (13–27)	69.4±10.4
White male	9 (78)	75.8±12.8	4.5	965	18 (17–20)	71.6±9.5
White female	28 (82)	73.9±11.9	11.5	864	32 (29–35)	74.1±11.4
Indian male	16 (100)	66.6±14.1	16.2	206	31 (24–38)	63.3±13.2
Indian female	41 (95)	64.4±12.2	46.4	180	60 (52–67)	60.8±12.8

* Cases and controls were 40 years old.
** Age-adjusted.

TABLE 2

Association between Gallstones and Gallbladder Cancer Expressed as RR in Various Populations

Sex	RR (95% Confidence Limits) among			
	Non-Indians			Indians
	Blacks	Whites	Total	
Male	2.8	6.9	4.3	–
	(0.9–9.0)	(2.0–23.3)	(1.8–7.8)	
Female	4.5	4.3	4.4	12.2
	(1.8–8.1)	(1.7–7.5)	(2.3–8.4)	(3.9–38.6)
Total	3.8	5.0	4.4	20.9
	(1.7–8.6)	(2.4–10.5)	(2.6–7.3)	(8.1–54.0)

From the estimated yearly incidence of gallbladder cancer in subjects with gallstones, we estimated the twenty-year cumulative risk of gallbladder cancer in subjects with untreated cholelithiasis. For all groups, this risk was less than 1 percent, with the exception of Native American Indian females, where the calculated cumulative twenty-year risk was 1.5 percent (95 percent CI = 1.3–1.8 percent).

When plotted on log-log coordinates, there was a strong relationship between the age-adjusted prevalence of gallstones and the age-adjusted incidence of gallbladder cancer in subjects 40 years. This relationship was well described by the equation $Y = 0.013 X^2$, where X = the age-adjusted prevalence of gallstones and Y = the age-adjusted yearly incidence of gallbladder cancer/100,000 in subjects 40 years of age ($r = 0.98$, $p = <0.001$) (figure 1).

Gallstone Growth, Size, and Risk of Gallbladder Cancer

As in the previous study [7], we found no difference between white and Black subjects with respect to any of the outcome measurements; therefore, these two racial groups were combined in the analysis to form one non-Indian group.

Mean age at cholecystectomy was 36.1 ± 15.5 SD years for Indians versus 41.2 ± 16.5 SD years for non-Indians (p = <0.001). In both groups, gallstone size appeared to increase with age, but Indian subjects were more likely than non-Indian subjects to have stones larger than 2 cm: age-adjusted odds ratio = 1.5, 95 percent CI = 1.2–2.0. The proportion of subjects with single stones, 20 and 22 percent, respectively, was similar in the two groups.

After plotting gallstone size against age, we used a regression technique to estimate gallstone growth. For Indians and non-Indians, the estimated growth rates, 0.19 and 0.21 cm per year, were similar. The overall estimate for growth after combining the two groups was 0.2 cm per year (95 percent CI 0.17–0.23 cm).

Lastly, we determined the risk of gallbladder cancer in relation to stone size, comparing stone size in 15 subjects with and 398 subjects 50 years without gallbladder cancer. Mean gallstone size in the gallbladder cancer patients was 2.5 ± 1.4 SD cm, as compared to mean stone size of 1.5 ± SD cm in subjects with benign gallbladder disease (p = <0.02). Table 3 compares gallstone size in subjects with and without gallbladder cancer after adjustment for age and race: Larger stones were more frequent in the cancer group, and there was a strong trend for increasing risk of gallbladder cancer with increasing stone size; chi-square for trend = 9.85, p = < 0.002. For subjects with the largest gallstones (± 3 cm), there was a ninefold increase in risk.

DISCUSSION

These studies serve to quantify the relationship between gallstones and gallbladder cancer and to help us understand why this rare tumor is so frequent in Native Americans. A reasonable hypothesis can be constructed as follows: Because of an underlying trait that may be genetic, Native Americans have a reduced metabolic rate and are prone to rapid weight gain when consuming a calorie-rich diet. The resulting obesity leads to gallstone formation [9,10], which in turn increases the risk of gallbladder cancer.

It would appear that the risk of cancer in American Indians with gallstones is much greater than for stone-bearing non-Indians. For other cancers with a suspected cause (e. g., lung cancer and smoking), the risk of disease is known to increase with duration of exposure. Native American subjects are known to develop gall-

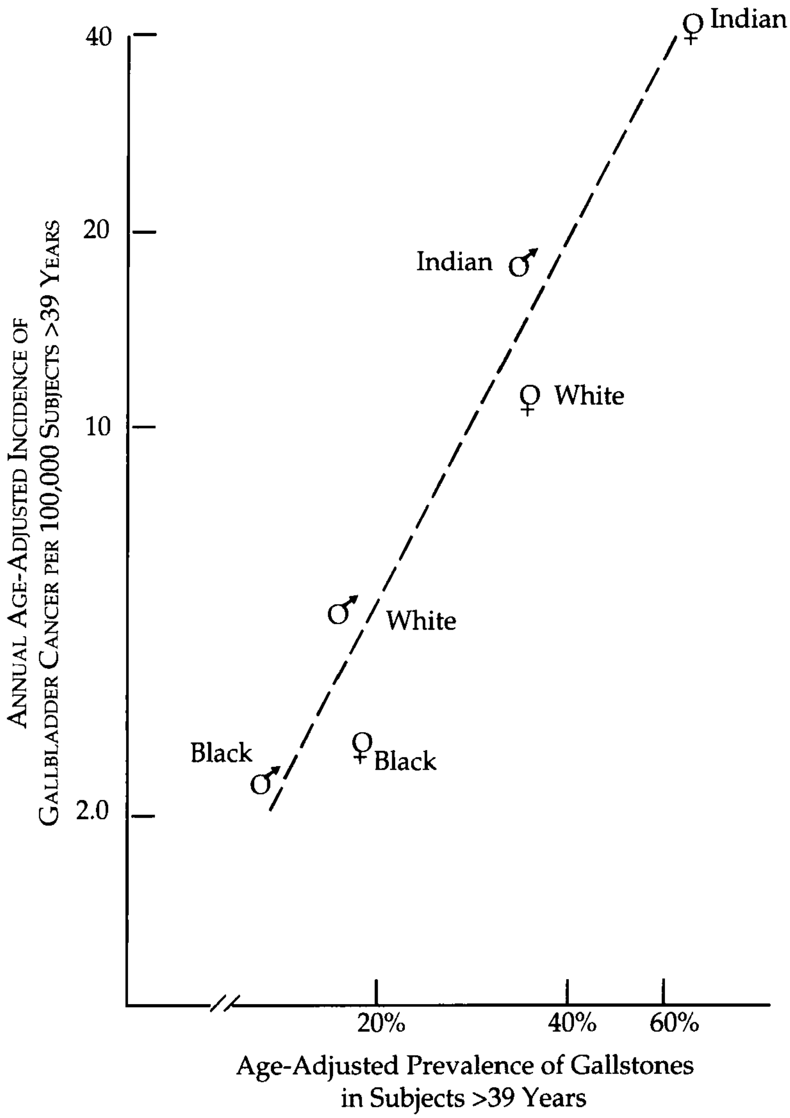

FIGURE 1. Scattergram showing relationship between gallstone prevalence and incidence of gallbladder cancer in subjects ≥40 years old. Log-Log coordinates ($r = 0.98$, $p = <0.001$).

TABLE 3

Number of Subjects 50 Years with and without Gallbladder Cancer in Relation to Gallstone Size

	Gallstone Size			
	<1 cm	**1–1.9 cm**	**2–2.9 cm**	**3 cm**
Cancer present	2	4	3	6
Cancer absent	133	152	71	42
Relative risk*	1	1.7	2.4	9.2
95% conficence interval	–	0.3–9.5	0.4–16	2.3–37

* Overall Mantel-Haenszel Risk adjusted for race. Chi square for trend = 9.85, p = <.002.

stones at a very early age [6]. Thus this population can be predicted to have a long duration of exposure to gallstones, the suspected causative agent.

As have the authors of a previous report, we have found an increased risk of gallbladder cancer in subjects with large gallstones [11]. One explanation for this finding could be that large stones imply longer duration of exposure, leading to an increased risk of cancer. Indeed, based on our own and another estimate of gallstone growth [12], it may take an extra one or two decades for the formation of large as compared to small gallstones.

A vexing public health problem concerns the management of the substantial population of Native Americans with undetected ("silent") gallstones. It would appear that considerably more than half of the females and about a third of the males harbor asymptomatic gallstones and therefore are at increased risk for gallbladder cancer. With increasing use of newer diagnostic techniques such as ultrasound, we can predict that many more subjects with gallstone disease will be detected during life than heretofore. The final decision with respect to management of these subjects must be made on an individual basis. Information now available concerning the risk of gallbladder cancer in subjects with untreated stones and about the relation of stone size to overall risk may be helpful. For example, large stones (2 cm or larger) in younger subjects may not be as harmless as has been reported [13]. Indeed, the estimated risk of this lethal tumor may be 5 percent or more for a young subject harboring a large gallstone and with an estimated additional fifty-year life expectancy. Development of newer surgical techniques such as laparoscopic cholecystectomy may make surgical treatment a more attractive option for such individuals than it has been heretofore.

ACKNOWLEDGMENT

I wish to thank D. Lowenfels for computer assistance.

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