RESEARCH ARTICLE

Comparison of Diets of Urban American Indian and Non-Hispanic Whites: Populations with a Disparity for Biliary Tract Cancer Rates

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Abstract

Aim: The incidnece of biliary tract cancer (BTC) is many-fold higher for American Indians (AI) relative to non-Hispanic whites (NHW). Neither gallstones nor genetics can account for this difference. There is speculation that certain fatty acids in bile may play a role in preventing BTC. Since diet may influence composition of bile, we compared the dietary intakes of urban AI and NHW adult women in New Mexico. Methods: Design, a cross-sectional study of the diets of lactating AI and NHW women was conducted. Setting, the University of New Mexico Hospital. Participants, healthy lactating women 18 to 39 years of age were recruited. Main outcome measures, a three-day diet record for each participant was analyzed. Results: The AI women consumed less calcium (p = 0.04) and significantly less short and intermediate chain-length fatty acids (C4-C12), but nearly twice as much proinflammatory arachidonic acid as the NHWs (p <0.01). The intake of dairy products by AI women was less than NHW women (p = 0.01) while the intake of processed meat products was higher (p <0.01). Conclusion: Dietary factors may account for the difference in the risk of BTC between AI and NHW women.

Keywords: Diet - calcium - intermediate chain fatty acids - dairy - biliary cancer - American Indian

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Introduction

Health disparities are defined as "differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States" (US Department of Health and Human Services 2002). Arguably the most remarkable health disparities in the United States is the difference in the incidence of biliary-tract cancers (BTC) between American Indians (AI) in the U.S. Southwest and Alaska and Non-Hispanic Whites (NHW) (Stuver and Trichopoulos, 2002). Malignancies of the biliary tract include those arising from the gallbladder, extrahepatic bile ducts (cholangiocarcinoma) and ampulla of Vater, and all three have a high rate of mortality. The incidence of biliary tract cancer is 7- to 25-fold more common in AI compared to NHW and this gap has persisted for decades (Fraumeni 1975; Espy et al., 2007). More recently, the disparity for gallbladder cancer has been shown to be more pronounced for AI residents of New Mexico where women have a gall bladder cancer rate nearly twice that of men (Barakat et al., 2006).

Although gallstones are common in indigenous North American populations and are a well-documented risk factor for biliary tract cancers, gallstones alone do not account for the high incidence of gall bladder cancer in AI. Although demographic considerations point to environmental and genetic factors, none has been identified with a high degree of certainty. Accordingly, the underlying basis for the ethnic disparity between AI and NHW with regard to biliary cancer remains obscure. A recent review of gallbladder cancer epidemiology made no mention of the role diet might play as a risk factor in this disease (Mehrotra, 2011). Furthermore, studies aimed at identifying possible dietary risk factors for BTC in AI in the U.S. Southwest are scarce. Information regarding the diets currently being consumed by the various AI sub-populations in New Mexico is scant. A report of nutrient intake of Navajo identified primary food sources of key nutrients: noteworthy were the findings that fat contributed about one-third of energy while fruits, vegetable and dairy products were each consumed less than once daily (Ballew et al., 2009). In a similar study of Pima Indians it was also found that fruits and vegetables did not make significant contributions to their diet and that "milk was not a favorite item" (Reid et al., 1971). Another study showed that dairy product intake among pregnant and lactating Navajo women revealing a median calcium intake of less than 60% of the Recommended Dietary Allowance (Butte et al., 1981). Dietary patterns in that population revealed a high intake of meat, processed meat, and lard with a low intake of fruits and vegetables. A recent study of the dietary intake of Navajo found that they frequently consumed processed meats such as hot dogs, bacon and

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sausages but only about half to one-third the Adequate Intake of calcium (Sharma et al., 2009). The low intake of calcium by AI has been attributed to the infrequent consumption of dairy products due in part because lactose intolerance is common and because of the perishability of dairy products. None of these studies of AI in the US Southwest included a direct concurrent comparison of the diets of AI with those of any other ethnic group in the Southwest, such as Hispanics or NHW.

In light of the fact that unsaturated fatty acids such as oleic, linoleic and α-linolenic acid have been shown to have inhibitory effects on cancer in animal models and cultured cells, we became interested in the diets of AI in our community, with particular focus on fatty acids (Serra et al., 2009). Others have speculated that free fatty acids in bile may play a role in preventing biliary tree cancers and that diet may influence the levels of these fatty acids in bile (Serra et al., 2009).

The aim of the present study was to compare the composition of the diets of AI and NHW adult women in New Mexico, with emphasis on fatty acids. We compared dietary records of AI and NHW women and found that the AI consumed significantly less calcium and certain intermediate chain fatty acids (e.g., caproic, caprylic, capric, lauric) and more arachidonic acid than their NHW counterparts. These observations confirm the findings of previous investigators that dairy products are currently not widely consumed by AI women and raise questions about the role constituents of dairy products might play in reducing the risk of biliary tract cancers.

Materials and Methods

Subjects

Women between 18 and 40 years of age who had been lactating for one to six months were recruited into a cross-sectional study while they were visiting clinics at the University of New Mexico Hospital. Exclusion criteria were maternal tobacco use, use of immunosuppressive drugs, pregnancy or diabetes mellitus. From June 2005 to February 2009 of the 789 mothers screened for eligibility, 304 were AI and 113 were NHW. Two-hundred-nineteen AI and 67 NHW women were determined to be eligible and invited to participate in the study. Of these, 199 AI and 43 NHW women were no longer breastfeeding, could not be reached, or were not interested in participating. Of the remaining, 20 AI and 24 NHW women enrolled in and completed the study. The socioeconomic status (SES) of the subjects was assessed by financial class based on Medicaid eligibility. Participant height and weight were measured using standard methods (Gordon et al., 1988). Body Mass Index (BMI) was calculated as kg/m^2.

Informed consent was obtained from each participant and the study was approved by the Human Research Review Committee of the University of New Mexico Health Sciences Center. Compliance with Health Insurance Portability and Accountability Act guidelines was maintained.

Dietary intake

Subjects were provided a standardized form along with written and verbal instructions about how to keep a diet record. Subjects recorded amounts of foods consumed in standard household measurements and completed the single written diet record of food and drinks consumed in the three days immediately preceding their clinic visit to the General Clinical Research Center.

At the clinic visit, a Registered Dietitian (RD) reviewed the participant's diet record and probed for consumption of any additional foods and drinks. Quantities of food were assessed and confirmed using Nasco Lifeform three-dimensional food models (Nasco Food Models, Modesto, CA). Information about brand names of foods and fats and oils used in cooking was collected. The 3-day diet records were coded, analyzed and reviewed by RDs using FIAS (Food Intake Analysis System, version Millennium 1.0, 2005, The University of Texas School of Public Health, Houston, TX). This software included foods consumed by AI. Averages of nutrients and food group information across the 3-day period were compiled from each participant's diet records.

During the clinic visit, the subjects presented containers of all dietary supplements they were currently taking. The label information was recorded onto a standardized form along with frequency of use. Subjects were questioned for any additional use of dietary supplements.

Statistical analyses

Data analysis was performed using the NCSS Statistical Software (NCSS, 2006, Kaysville, UT). Data are presented as the mean and standard deviation, except for those parameters with non-normal distributions. These are presented as the median (minimum-maximum). Group comparisons were made using the two-sided t-test. Percentages were compared using the test of proportions for two independent variables. A p-value of 0.05 was considered as significant.

Results

Subject differences

Demographic information is summarized in Table 1. Subjects ranged in age from 18 to 39 years. Of the AI women, 17 resided in the Albuquerque area and 3 in small towns; none resided on an Indian reservation. All of the NHW women resided in the greater Albuquerque area. Significant differences between the groups were seen for age, height, BMI, and SES. American Indian subjects were younger and of lower SES. Mean body mass index of the AI group was categorized as "overweight"; NHW mean was "normal weight" (US Department of Health and Human Services, 2011).

Three-day diet record assessment

Mean intakes of macro- and micro-nutrients from food sources for both groups are compared in Table 2. Of the 52 nutrients reported by FIAS, only 10 were significantly different between the AI and NHW subjects. With regard to macronutrient consumption, the AI women consumed more carbohydrate but similar amounts of energy, fat and protein as the NHW subjects. There was no significant difference between mean percent energy as fat.

There were no differences between the two groups

Table 1. Characteristics of the American Indian (AI) and Non-Hispanic White (NHW) Women

	AI (n=20)	NHW (n=24)	p-value
mean±SD:			
Age (yrs)	23.6±4.5	31.4±4.2	<0.01
Height (cm)	161.6±6	166.0±5	< 0.01
Weight (kg)	75.3±15.5	67.4±10.6	0.05
BMI (kg/m^2)	29.1±5.5	24.6±4.2	<0.01
Percent of subjects:			
Low socioeconomic status	90	42	<0.01
Using dietary supplements	45	79	0.02

Table 2. Intake of Selected Nutrients Obtained from Food Sources from 3-day Diet Records of Lactating AI and NHW Women as Compared to the Dietary Reference Intake

Nutrient	AI (n=20) Mean±SD	Percent of subjects with intake <EAR*	NHW (n=24) Mean±SD	Percent of subjects with intake <EAR*	p value
Energy (kcal)	2400 ± 569	NA†	2100 ± 528	NA†	NS††
Protein (g)	96.5 ± 31.9	30	86.9 ± 25.7	20.8	NS††
Carbohydrate (g)	302 ± 75	0	255 ± 58	4.2	0.02
Fat (g total)	91.9 ± 25.8	NA†	86.3 ± 32.8	NA†	NS††
Saturated fat (g total)	30.7 ± 9.7	NA†	30.7 ± 12.1	NA†	NS††
C 4:0 (mg)	554 ± 360	NA†	816 ± 445	NA†	0.04
C 6:0 (mg)	277 ± 197	NA†	403 ± 216	NA†	0.05
C 8:0 (mg)	186 ± 115	NA†	347 ± 161	NA†	<0.01
C 10:0 (mg)	417 ± 255	NA†	656 ± 311	NA†	<0.01
C 12:0 (mg)	552 ± 303	NA†	1210 ± 600	NA†	<0.01
Monounsaturated fat (g)	35.4 ± 10.3	NA†	32.2 ±12.5	NA†	NS††
Polyunsaturated fat (g)	18.3 ± 6	NA†	17.1 ± 8.7	NA†	NS††
Vitamin A (RE total)	1150 ± 466	NA‡	1380 ± 600	NA‡	NS††
Vitamin A (IU total)	7590 ± 4270	NA‡	9440 ± 5320	NA‡	NS††
Thiamin (mg)	1.97 ± 0.61	5	1.91 ± 0.75	12.5	NS††
Riboflavin (mg)	2.22 ± 0.73	10	2.34 ± 0.74	4.2	NS††
Niacin (mg)	27.6 ± 10.2	0	22.6 ± 7.04	8.3	NS††
Vitamin B-6 (mg)	2.16 ± 0.68	30	2.01 ± 0.70	37.5	NS††
Folate (mg)	433 ± 143	60	420 ± 112	62.5	NS††
Vitamin B-12 (μg)	5.19 ± 1.68	0	5.21 ± 3.25	8.3	NS††
Vitamin C (mg)	160 ± 144	35	109 ± 69	54.2	NS††
Vitamin D (μg)§	3.36 ± 3.00	100	4.80 ± 4.67	75.0	NS††
Vitamin E (ATE)	9.07 ± 2.91	100‖	11.2 ± 5.04	87.5‖	NS††
Calcium (mg)	940 ± 388	35	1250 ± 563	20.8	0.04
Magnesium (mg)	308 ± 77	25	370 ± 119	20.8	0.05
Iron (mg)	19.7 ± 6.6	0	17.3 ± 4.7	0	NS††
Copper (mg)	1.43 ± 0.37	15	1.57 ± 0.57	16.7	NS††
Zinc (mg)	14.4 ± 4.4	20	13.7 ± 4.8	25.0	NS††
Selenium (μg)	134 ± 52	0	106 ± 26.6	0	0.02
Arachidonic acid (mg)	191 ± 121	NA†	113 ± 66	NA†	<0.01
Eicosapentaenoic acid (mg)	39.5 ± 115	NA†	28.8 ± 96.9	NA†	NS††
		Percent of subjects with intake <EAR* Adequate Intake¶		Percent of subjects with intake <EAR* Adequate Intake¶	
Linoleic acid (g)	16.1 ± 5.26	25	15.1 ± 7.7	58.3	NS††
Linolenic acid (g)	1.50 ± 0.51	35	1.61 ± 1.01	58.3	NS††
		Percent of subjects with intake <EAR* Recommendation**		Percent of subjects with intake <EAR* Recommendation**	
Docosahexaenoic acid (mg)	75 ± 130	90	60.4 ± 133	95.8	NS††

*EAR: Estimated Average Requirement (EAR for age and life stage group of lactation), †NA: Not available, ‡Cannot convert to mcg Vitamin A from units of measure reported by FIAS Me 1.0, §Calculated from fluid milk, fortified cereal, and seafood, ‖Calculated as alpha tocopherol equivalent (ATE) x 0.8, ¶Adequate Intake for age and life stage group of lactation, **As compared to 200 mg daily recommendation for lactating women[16], NS: not significant

Table 3. Pyramid Servings of Food Groups from 3-day Diet Records Obtained from AI and NHW Women*

Food Group	AI** (n=20)	Range	NHW** (n=24)	Range	p value
Dairy (total servings)	1.42	0.37-4.42	2.18	0.68-7.56	0.01
Cheese (servings)	0.57	0-2.32	0.85	0.01-2.87	NS†
Milk (servings)	0.65	0-3.39	1.09	0.21-4.69	NS†
Yogurt (servings)	0	0-0.47	0	0-1.24	NS†
Fruit (total servings)	1.55	0.07-7.99	1.36	0.05-3.72	NS†
Citrus, melon, berry (servings)	0.64	0-7.96	0.56	0-2.60	NS†
Other fruit (servings)	0.56	0-2.80	0.81	0-2.71	NS†
Vegetables (total servings)	3.05	1.0-5.63	3.33	0.5-8.91	NS†
White potato (servings)	1.06	0-2.65	0.25	0-3.47	NS†
Dark leafy green (servings)	0.02	0-2.20	0.23	0-2.31	NS†
Deep yellow (servings)	0.07	0-0.79	0.06	0-1.40	NS†
Tomato (servings)	0.35	0-1.70	0.55	0-4.15	NS†
Grains (total servings)	8.62	5.0-17.8	6.64	3.82-11.7	<0.01
Whole grains (servings)	1.67	0-4.07	1.52	0.09-5.48	NS†
Non-whole grains (servings)	6.45	3.40-15.9	5	2.16-8.23	<0.01
Meat (including poultry, fish and alternatives)					
Meat (total servings)	2.22	1.20-6.52	1.86	0.28-3.49	0.01
Lean meat, poultry, fish (total oz.)	4.64	2.44-14.5	2.99	0-7.10	<0.01
Lean meat from processed (oz.)	0.95	0-3.77	0	0-1.57	<0.01
Beef, pork, lamb (oz.)	2.45	0.95-4.84	1.22	0-4.45	<0.01
Poultry (oz.)	0.69	0-10.9	0.93	0-5.13	NS†
Fish, other seafood (oz.)	0	0-6.41	0	0-2.29	NS†
Lean meat equivalent eggs (oz.)	0.34	0-2.32	0.45	0-1.87	NS†
Lean meat equivalent dry beans (oz.)	0	0-0.50	0.04	0-1.32	NS†
Lean meat equivalent nuts, seeds (oz.)	0.07	0-0.57	0.23	0-3.84	NS†
Added sugars (teaspoons)	22.8	0.32-41.5	15.8	6.57-32.90	0.05
Discretionary fat (grams)	67.5	32.2-96.7	65.3	23.2-150.60	NS†

*To calculate pyramid servings of food groups, FIAS Millennium 1.0 uses "Pyramid Serving Database for USDA Survey Food Codes (Version 1)", **Median/Day, †NS: not significant

for intake of water-soluble or fat-soluble vitamins from food sources. For minerals and trace elements, the AI consumed significantly less calcium and magnesium and more selenium from food sources than NHW subjects. Calcium intake for AI subjects ranged from 367-1840 mg while the NHW range was 379-2750 mg (p = 0.04). The AI group consumed significantly less of short and intermediate chain-length fatty acids, namely butyric acid (C4:0), caproic acid (C6:0), caprylic acid (C8:0), capric acid (C10:0) and lauric acid (C12:0), but significantly more arachidonic acid (20:4n-6) from food sources than NHW. No differences were found in the intakes of any of the omega-3 fatty acids, namely eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) or α-linolenic acid from food sources by the two groups.

Using a cut-point method, both groups of women had intakes of certain nutrients that were below the Estimated Average Requirement (Table 2) (National Academy of Sciences, 2004). A significantly lower intake of calcium from food sources was seen in the AI group as compared to NHW. The AI group showed a lower, but non-significant, intake of vitamin D as compared to NHW (Calvo et al., 2004; Agricultural Research Service, 2009). Ninety percent or more of all subjects had an inadequate intake of DHA (Glew et al., 2011).

Table 3 compares the food sources of the two groups using USDA pyramid servings. Although both groups showed similar median total fruit intakes, the AI group consumed 42% of fruit servings as fruitades and drinks as compared to 6% for NHW. Significant differences in food group intake between AI and NHW were found for dairy and grain servings, meat servings (including processed meat) and teaspoons of added sugar. As compared to the

NHW, the AI exhibited a significantly lower intake of dairy products and a higher intake of meat (excluding poultry and fish) and added sugar. Total consumption of processed meat products was significantly higher for AI ($p < 0.01$).

Overall dietary supplement usage was significantly higher among NHW subjects (Table 1). Sixteen NHW women took a multiple vitamin/mineral type dietary supplement as compared to eight AI.

Discussion

Although several comprehensive studies of the dietary habits of AI in the US Southwest have been reported within the last three decades, none provides a concurrent comparison of the diets of AI and NHW (Reid et al., 1971; Butte et al., 1981; Ballew et al., 2009; Sharma et al., 2009). Furthermore, lacking are published reports aimed at investigating the contribution dietary factors might make in explaining the extraordinarily high incidence of BTC in AI. In a review of the literature which addressed risk factors for gallbladder cancer globally, including dietary habits, Strom and colleagues found that baking foods and using pork fat in cooking were risk factors for gallbladder cancer (Strom et al., 1995). Dairy products were not mentioned in that review. Nevertheless, it is widely accepted that constituents of food, such as calcium and vitamin D, may be protective against cancer (Huth et al., 2006).

The main result of the present study was that the AI women consumed significantly less dairy products than the NHW women. Three-day dietary records revealed that the intake of calcium and intermediate chain-length fatty acids by the AI subjects was significantly below that of the NHW group (Table 2). The major food sources of these nutrients are milk, yogurt and cheese (US Department of Agriculture, 2010). Our hypothesis that the AIs in our study were consuming less dairy products than the NHW was borne out by our analysis of food groups (Table 3), where we found that the AI consumed only about 65% as much dairy product as the NHW.

Thirty-five percent of AI subjects had a dietary intake from food sources that was below the EAR for calcium as compared to about one-fifth of NHW. This reflects striking food choice differences and hence nutrient intake differences between groups. Low consumption of dairy products in AI populations has been previously documented historically and currently (Reid et al., 1971; Butte et al., 1981; Ballew et al., 2009; Sharma et al., 2009). Lactose intolerance has been reported to be high in AI populations and estimated to be at a 50% higher incidence by adulthood as compare to other populations (Wilt et al., 2010). Dairy products naturally contain lactose, with fluid milk being a high source and yogurt and hard cheeses containing lesser amounts (US Department of Agriculture, 2010). Use of lactose-free/reduced dairy products may be a way for AI women to increase dairy product intake or use of a lactase supplement. Perishability has been cited as a reason for low dairy product intake by AIs. Use of shelf-stable dairy products may be a solution. Intermediate chain-length fatty acids (ICLFA) occur in higher concentrations in regular fat dairy products as opposed to low and non-fat varieties; non-fat milk contains approximately 5% or less of the ICLFA as found in whole milk (US Department of Agriculture, 2010).

As compared to the NHW group, the dietary pattern seen in the AI exhibited more characteristics of the "less healthy pattern" that has been associated with the development of colorectal cancer (Miller et al., 2010). The AI women showed a lower intake of fruit and vegetables and a higher intake of processed meats, red meat, and refined carbohydrates as compared to NHW. The AI consumed significantly more processed meat than NHW women. Processed meat consumption has been reported to increase the risk of development of other gastrointestinal tract cancers such as colorectal cancer, however a recent report showed that this may not be a strong association (Alexander et al., 2010; Miller et al., 2010). The AI had significantly higher BMI than NHW. An association between high BMI and risk of development of gallbladder cancer has been reported (Strom et al., 1995). Although both groups showed food source intakes of vitamins and minerals below the EAR cut-point, the AI were less likely to take vitamin and mineral-containing supplements than NHW (Table 1).

We judge the most interesting result of our comparative study of the diets of AI women and NHW women to be the finding that the intake of calcium and ICLFA was much lower in the AI group relative to the NHW group (Table 2). It is reasonable to ask: What do calcium and ICLFA have in common with regard to human food sources? A reasonable answer to this question is dairy products. The high content of calcium and ICLFA in milk and processed milk products such as butter, cheese, and yogurt is well-documented and widely recognized (US Department of Agriculture, 2010). The AI subjects did in fact consume dairy products less frequently than NHW subjects.

Prostaglandins play a key role in inflammation and inflammation has been implicated in the pathogenesis of cancer. Prostaglandins are formed when arachidonic acid is released from membrane phospholipids by phospholipases and metabolized by PGG/H synthase or cyclooxygenase and their respective synthases (Ricciotti and FitzGerald, 2011). Our finding of a higher intake of the pro-inflammatory omega-6 fatty acid, arachidonic acid in the AI women raises questions about what effect higher levels of this substrate for COX-2 might have on the production of PGE_2 and other prostanoids that have been implicated in various aspects of the biology of cancer.

In the case of cholangiocarcinoma, a malignant epithelial neoplasm of the biliary tree, the tumor is thought to arise from a condition in which there has been long-standing inflammation mediated primarily by prostaglandin E_2 (PGE_2), which is derived by cyclooxygenase-2 (COX-2) acting on the proinflammatory fatty acid substrate, arachidonic acid (Mahli and Gores, 2006). "In vitro" studies using cholangiocarcinoma cells showed that exogenous PGE_2 increases tumor cell growth, while selective inhibitors of COX-2 prevent the growth and invasivity of cholangiocarcinoma cells "in vitro" and in nude mice (Sirica et al., 2002; Lai et al., 2003).

In relating our findings to the disparity in BTC between AI and NHW, it is tempting to search for possible pathophysiologic links between calcium, and one or more of the three types of biliary tract malignancies that are so very much more common in AI populations in the US Southwest. For example, since calcium is a second messenger in numerous intracellular signaling pathways related to the control of cell proliferation, it is reasonable to speculate that the decreased dietary intake of calcium by AIs might compromise pathways involved in regulating cell growth or the invasivity of cancerous cells. Calcium and dairy product intake has been identified as a determinate of chronic disease and health throughout life, including a possible association with cancer risk (Key et al., 2002; Nicklas 2003; World Health Organization 2003,). Although it is tempting to speculate about possible contributions a low calcium or ICLFA intake or increased arachidonic acid intake might make to increasing the risk of BTC, we believe it is both reasonable and advisable to keep an open mind and entertain the possibility that a low intake of biomolecules other than calcium or certain fatty acids in milk and dairy products in general may ultimately help explain why the incidence of biliary tract cancers are so very high in AI. Dairy products and ICLFA in particular may simply be markers for other molecules that protect against BTC.

A limitation of this study is that the subjects were a small group of women. Furthermore, since all of the women resided in urban areas, the results may not reflect the usual dietary intake of AI who reside on reservations. Information was not collected regarding tribal affiliation for whom BTC rates may vary. The two groups of women in the current study differed significantly for age, BMI and SES. These factors may affect dietary intake and contribute to study limitations.

Future studies should include a case-control study of the dietary habits of patients with BTC compared to age- and gender- matched healthy controls. Also assessment of arachidonic status, which can be accomplished by analyzing red cell or serum phospholipids for content of arachidonic acid, should be considered.

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