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Lynch Syndrome II in a Navajo Family: A Revisit

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ABSTRACT

A study of variation in cancer incidence among the Navajo Indians, given their relative racial and environmental homogeneity, could provide important clues to etiology and, ultimately, to cancer control. A family with Lynch syndrome II, which was originally described in a Navajo kindred, has received follow-up eight years later. Three at-risk relatives have had newly diagnosed colorectal cancer. These findings were highly predictable, given knowledge of the natural history and genetics of this autosomal dominantly inherited disorder. This disorder is believed to be the first example of hereditary colorectal cancer of any type among American Indians. Given the ubiquitous nature of hereditary colorectal cancer disorders, it is likely that other, similar, colorectal cancer-prone families exist among the Navajo. Biomolecular tech-

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nology employing DNA analysis, when it becomes available, should aid in cancer genetic diagnosis. Meanwhile, knowledge of hereditary colon cancer's natural history, coupled with painstaking compilation of the pedigree, will be mandated for hereditary colorectal cancer syndrome diagnosis.

INTRODUCTION

Throughout the world, there is marked variation in the pattern and distribution of cancer of specific anatomic sites [1]. Several striking examples are as follows: (a) the occurrence of nasopharyngeal carcinoma excess in the Caspian Littoral and in areas of mainland China, and in Chinese immigrants residing in Singapore, Hong Kong, Shanghai, Hawaii, and California (who show a higher incidence of this disease than their non-Chinese counterparts); (b) the paucity of Ewing's sarcoma in Blacks; (c) the low incidence of chronic lymphocytic leukemia in Japan; (d) the relatively constant incidence of Wilms' tumor in virtually all reporting centers throughout the world; and (e) the many examples of hereditary cancer syndromes involving cancer of variable anatomic sites. The American Indians' experience with cancer should be added to this list. In-depth study of these experiments of nature and nurture could aid in the elucidation of cancer's etiology and promote interest in its control.

Variation in cancer incidence among Indians of North America has been a subject of interest among several cancer genetic/epidemiologists. Particularly noteworthy have been the pioneering investigations of Lanier and her colleagues [2,3] among Eskimo, Indians, and Aleut in Alaska. These landmark studies led to the identification of increased risks in Alaska Natives for nasopharyngeal, salivary gland, kidney, gallbladder, and liver cancers. These contrast to the observed decreased risks for cancers of the lung, larynx, urinary bladder, prostate, breast, corpus uterus, malignant melanoma, and lymphoma among that Alaskan population. Studies by Lanier and her colleagues of primary liver cancer [4] and esophageal cancer [5] among these groups have clearly shown how knowledge of genetic epidemiology of cancer can lead to the understanding of etiology, pathogenesis, and control. This work is pertinent because the Navajo Indians are a subgroup of the Athabascan linguistic group that migrated into the southwestern United States from eastern Alaska and Canada

about 1000–1200 A. D. [6]. About 150,000 Navajo reside in New Mexico and Arizona. For the most part, these individuals live on reservation lands and have undergone relatively little genetic admixture with other ethnic groups.

The study of family history and lifestyle among American Indians could lead to elucidation of important clues concerning the relative strength of specific environmental effects v. host factors in cancer's etiology, an area of intense interest to cancer genetic epidemiologists. Clearly, we must never consider genetic and environmental factors as acting independently, i. e., as if they were wholly isolated events. Studies of the interaction of these factors, many of which could be initiated by knowledgeable clinicians at the "bedside" and then abetted through the multidisciplined efforts of biostatisticians, epidemiologists, geneticists, and biomolecular geneticists, would then enable rapid and cost-effective solutions to cancer etiology and control.

Our purpose is to provide an update of an extended Navajo Indian kindred [7] (table 1) which has shown an excess of colorectal cancer with a pattern of autosomal dominant transmission in the absence of familial adenomatous polyposis (FAP). The findings are consistent with Lynch syndrome II [8].

MATERIAL AND METHODS

Hereditary colorectal carcinoma is broadly classified into FAP and hereditary nonpolyposis colorectal cancer (HNPCC). HNPCC is further subdivided into Lynch syndromes I and II. Lynch syndrome I is characterized by an autosomal dominantly inherited predisposition to site-specific colorectal cancer with proximal predominance, an excess of synchronous and metachronous cancer of the colorectum, and early age of cancer onset. Lynch syndrome II contains all of the colorectal cancer features of Lynch syndrome I but, in addition, shows an excess of extracolonic primary cancer, particularly carcinoma of the endometrium and ovary [8] and, in some families, carcinomas of the breast [9], stomach [10], small bowel [11], pancreas [12], and urological system [13].

Our first contact with this Navajo family occurred in 1980–81 through a query from a public health surgeon (TD) who had recognized the possibility that the genetic diagnosis of Lynch syndrome II could explain the cancer excess among them. Ques-

TABLE 1

Tumor Table for Family #7 (12/5/89)

Ind #	Site	Histology	Age @ Dx	Source
II-14	Stomach	Carcinoma	41	DC
III-4	Stomach	Adenocarcinoma	52	PR
III-11	Ascend colon	Adenocarcinoma	40	PR
	Rect/Sig	Adenocarcinoma	43	PR
III-12	Splenic flex	Adenocarcinoma	34	MR
III-13	Hepatic flex	Adenocarcinoma	29	PR
III-14	Splenic flex	Adenocarcinoma	45	PR
*III-15**	*Descend colon*	*Adenocarcinoma*	*54*	*PR*
III-18	Cecum	Adenocarcinoma	39	PR
	Ascend colon	Adenocarcinoma, in polyp	39	PR
III-19	Trans colon	Adenocarcinoma	33	PR
IV-8	Ascend colon	Adenocarcinoma	23	PR
IV-12	Ovary	Serous cystadenocarcinoma	40	PR
	Ascend colon	Adenocarcinoma	41	PR
*IV-14**	*Sigmoid*	*Adenocarcinoma*	*41*	*PR*
*IV-19**	*Sigmoid*	*Adenocarcinoma*	*31*	*PR*
	Rectum	Adenocarcinoma	31	PR

* Italics = newly diagnosed cancers since original family ascertainment in 1980–81.

tionnaires were circulated to the proband, who had recently been diagnosed with a papillary serous cystadenocarcinoma of the ovary, and to her key relatives. Permission was obtained for retrieval of primary medical and pathology documents. Visits were conducted in 1982 and 1989 by our research team to the Public Health Service Hospital in Tuba City, Arizona, which is in geographic proximity to where many of the family members reside. More than one hundred relatives were seen during these visits. They were divided into small groups of about ten to fifteen individuals, thereby enabling a more personal educational experience. During these sessions, the important natural history features of colorectal cancer occurrence within the family were described, and the significance of the family history of cancer was covered in detail, inclusive of the genetic risk status of each individual. A free-wheeling question-and-answer period allowed the patients to ask questions. These dynamic, group therapy-oriented sessions appeared to help break down barriers to communication. In addition, it also permitted the relatives to reflect on events in the family that often led to our obtaining new genealogic and medical information relevant to cancer occurrence in the kindred.

Venous blood and minuscule skin biopsies were obtained to extract DNA for a variety of biomolecular/genetic investigations. Screening colonoscopies or flexible sigmoidoscopies were performed on seventeen individuals. Colonic mucosal biopsies were obtained at each area of the colon for tritiated thymidine and bromodeoxyuridine labeling studies of the colonic crypt compartments. A subset of these colonic mucosal biopsies were snap-frozen for DNA studies, and others were fixed in formalin for microscopic investigations. These studies are still in progress and will be the subject of a future publication.

RESULTS

Eleven patients (six males, five females) in the pedigree manifested histologically verified colorectal carcinoma, three of whom had two verified, separate primary colonic cancers. Their ages ranged from 23 to 54, with an average age onset of 37.5. Nine out of fourteen colonic lesions (64.29 percent) from eight of the eleven patients (72.73 percent) were located in the right colon.

Three patients (III-15, IV-14, IV-19) have manifested colorectal

cancer (all histologically verified) since our visit to Tuba City in 1982 (table 1). Each of these patients had been initially seen by us during our visit in 1982 and participated in the educational program. Only two of these patients (III-15, IV-14) were known to have had any colorectal cancer surveillance. This comprised only stool guaiac determination with negative findings one year and two years, respectively, prior to their cancer diagnoses.

In 1987, at age fifty-four, patient III-15 presented with anemia and an acute "gastrointestinal hemorrhage." She reportedly did not have any prior signs or symptoms. A barium enema revealed a probable carcinoma of the descending colon. The surgeon was aware of her family history, and thus he performed an almost total colectomy. The diagnosis was poorly differentiated, infiltrating adenocarcinoma of the descending colon, infiltrating through the muscular wall into the surrounding serosal adipose tissue. Four out of seven mesenteric nodes were positive for metastatic adenocarcinoma. She is currently alive without symptoms.

This patient's daughter (IV-19), age thirty-one, presented with hemoccult positive stools and diarrhea approximately two months following her mother's colorectal cancer diagnosis in 1987. We are not aware of any prior screening examinations of her colorectum. A barium enema disclosed two large, fungating masses in the distal sigmoid colon and proximal rectum. Of interest was the presence of "myriad" small (1 cm) polyps in the right colon. Again, knowing the significance of her family history, the same surgeon performed a near total colectomy with anastomosis of the ileum to the rectum. The pathology report described a 4x2.8x1 cm mass approximately 66 cm from the cecum. Approximately 4.5 cm from this lesion, a similar lesion (4.5x4x1 cm) was present. Both lesions were diagnosed as adenocarcinomas, well-differentiated, infiltrating into the mesenteric adipose tissue. Nineteen pericolic lymph nodes were negative. She is still surviving and remains symptom-free.

The third patient, IV-14, at age forty-one, saw his physician because of "fatigue and cough" and reported also that he had noted rectal bleeding. He had last been seen by his physician two years earlier, at which time his stool was guaiac negative. A flexible sigmoidoscopic examination to 28 cm disclosed an inflammatory mass lesion. This was followed by barium enema, which revealed a typical-appearing core lesion of the sigmoid colon. A sigmoid-colectomy was performed with a low anterior resection with direct anastomosis. The pathology showed a 5.5x3.3 cm mass extending through the bowel wall into the pericolic fat. The

diagnosis was well-differentiated adenocarcinoma, arising in a tubulovillous adenoma. This was described as a Duke's B2 lesion.

A point of keen interest was that during the colonoscopic examinations on all of the seventeen patients we evaluated, the colons had a marked paucity of polyps. Indeed, only two of the patients were found to have isolated adenomatous polyps. One of the children (IV-16) of affected individual III-12 has an inflammatory polyp in the proximal transverse colon, while patient IV-14 had a tubular adenoma in the descending colon. These findings provide added credibility to diagnosis of the colonic phenotype being consistent with HNPCC.

DISCUSSION

Given the lack of premonitory physical signs and/or biomarkers of Lynch syndrome genotype status, the physician must rely on knowledge of the family history of colorectal cancer in concert with those salient characteristics of its phenotype. This information, once assembled in the pedigree, can provide powerful and cost-effective approaches to cancer control. In an autosomal dominantly inherited syndrome predisposing to colorectal cancer such as the Lynch syndromes, the colorectal cancer risk to first-degree relatives of a colorectal cancer-affected individual will approach 50 percent. Cancer predictability can then be highly targeted to the colon on integrally related organs which characterize the particular hereditary syndrome.

HNPCC is now recognized as constituting a highly significant statistical fraction of the overall colorectal cancer burden. Based on anecdotal information during more than two decades of its study, Lynch et al. [14,15] predicted that 5 to 6 percent of all cases of colorectal cancer would fulfill the criteria for HNPCC. More recently, Mecklin and colleagues [16–18] have studied HNPCC from tumor registry data in Finland. Mecklin's most recent estimate [19] of the frequency of HNPCC involved the study of all colorectal cancer patients (N = 468) who were diagnosed in one Finnish county (250,000 inhabitants) during the period 1970–79. It is of interest that HNPCC emerged as the most common verifiable risk factor for colonic cancer, involving 4 to 6 percent of all colorectal cancer patients identified in this study. In contrast to these findings, the frequency of familial adenomatosis and ulcerative colitis in this population was only 0.2 percent and 0.6 percent,

respectively. Since HNPCC lacks distinguishing physical signs and/or biomarker(s) that clearly aid in the depiction of genetic risk status, one must rely heavily on extended pedigree studies for its recognition.

The Navajo Indians are of particular interest from the standpoint of cancer occurrence, because they show remarkably high rates of gallbladder cancer in the face of a marked paucity of colorectal cancer [20,21,22]. In a comparison study of cancer primary sites by rates as obtained from death certificates in the United States, 1950–67, Sievers found that colon cancer in American Indians was only 44.3 percent of the rate for the Caucasian population [22]. Of 155 cases of cancer in the Indians of the Southwest during 1954–61, only five involved the colon [23]. In another investigation, only 14 percent of cancers involving the gastrointestinal tract in Navajos originated in the large bowel [24]. In an autopsy study of Southwestern Indian tribes, only one case of colon cancer was found among 53 malignant neoplasms, 21 of which originated in the gastrointestinal tract [25].

So far as we can determine, this Navajo family is the only example of hereditary colorectal cancer of any type among American Indians [7]. Undoubtedly, other similar families exist among this population, inclusive of the Navajo, since hereditary colorectal cancer disorders appear to be ubiquitous throughout the world [26]. The study of hereditary colorectal cancer in affected and at-risk Navajo patients, who have resided for virtually all of their lifetimes in the same geographic area, could provide a rather unique opportunity to investigate colonic cancer's etiology and pathogenesis. Emphasis should be given to lifestyle, particularly dietary patterns, in concert with family history of cancer.

While the focus of attention has been on hereditary colorectal cancer, it is important to call attention to the need to consider the role of hereditary factors in *all* forms of cancer among the Navajo. Unfortunately, this subject has received only limited attention. One such example was the finding of an apparent excess of retinoblastoma in Navajo Indian children [27]. Two of six cases of retinoblastoma showed bilaterality. The presence of bilaterality, in accord with Knudson's hypothesis, is consistent with the *genetic* as opposed to the *sporadic* variant of retinoblastoma. However, even the presence of unilateral disease does not exclude a previously unexpressed gene for retinoblastoma. Intensive ophthalmological screening of infants and children who are first-degree relatives of patients with retinoblastoma, including screening of

the contralateral eye among those affected with unilateral retinoblastoma, is mandatory for effective cancer control. A recommended surveillance program should include indirect ophthalmoscopy every three months until two years of age. This may then be reduced to every four months until age four years and then to every six months until the age of ten years. It is clear that the logical sequel to identification of *any* hereditary cancer syndrome is *surveillance* of high-risk relatives.

This same logic applies to the Navajo Lynch syndrome kindred that is the subject of this report. In short, given the knowledge that has been accrued about the need for surveillance in the Lynch syndromes, all at-risk relatives from this family should be provided with the following: (a) initiation of intensive education by the late teens; (b) fecal occult blood screening by age twenty; and (c) initiation of colonoscopy at age twenty-five, with repeat of this procedure every other year through age thirty-five, and then annually thereafter. Flexible sigmoidoscopy will not suffice, given the cancer predilection to the right colon [14,26]. In the absence of expertise in colonoscopy, barium enema should be performed. These minimal recommendations could provide excellent prospects for improving cancer control. However, so far as we can determine, there has not been *any* funding allocated for these cancer control pursuits in this family. In turn, there are no funds available for case finding, although we have evidence that the family is extensive; our group has identified the segregation of colonic cancer in only one portion of the kindred. Predictably, this life-threatening trait could be segregating in other branches of the family. Unfortunately, case findings will only be of academic interest if funds for education and surveillance are unavailable.

While we have stated that this is the *first* recognition of the Lynch syndromes in the Navajo Indian population, it is important to realize that the compilation of cancer family history remains notoriously neglected in the workup of all patients, including American Indians. Thus, other examples of hereditary colorectal cancer, including FAP and the Lynch syndromes, may have been missed due to lack of attention to the family history. It also follows that knowledge of cancer genetics among physicians needs to be upgraded, given the frequent failure to consider the natural history of hereditary cancer in surveillance of patients at increased genetic cancer risk. Undoubtedly, these shortcomings are a product of traditional medical education wherein environmental factors are often considered the *sole* cause of cancer and genetics are

ignored. Attention is often restricted to the individual patient, with neglect of his/her relatives who are potentially at risk for cancer.

In future studies of colorectal cancer epidemiology among the Navajo Indians, it will be important to realize that regardless of any potential exogenous carcinogenic exposures that might be discovered in the environment of these patients, only a fraction of those exposed to any given carcinogen will develop colorectal cancer. Why is it then that so many patients with heavy carcinogenic exposure remain cancer-free? A plausible explanation of this phenomenon is that the genotype controlling cancer *expression* variably predisposes to *resistance* as well as *susceptibility* to cancer. This phenomenon has been clearly recognized at the infrahuman level since the turn of the century and has only recently been appreciated in humans, where the extraordinary interhuman variability in susceptibility to carcinogens, consonant with the concept of ecogenetics, has been identified. For example, research in the laboratories of Harris and associates [28,29] at the National Cancer Institute has shown that binding levels of benzo[a]pyrene to DNA vary from fifty- to one hundredfold in cultured human cells. This enormous variation in carcinogen interaction with human cells may be attributed to the fact that the majority of chemical carcinogens require enzymatic activation, and thus host factors play a major role in determining variation in such enzyme capability [29].

In conclusion, we have provided an update of colorectal cancer in a Navajo family with a phenotype that is consonant with the diagnosis of Lynch syndrome II. Undoubtedly, many others with differing forms of hereditary cancer are awaiting discovery among the Navajo. The reward of such cancer genetic diagnoses could be a reduction in morbidity and mortality through implementation of available cancer control strategies. These efforts will be abetted significantly once the gene for the Lynch syndromes has been identified and DNA-polymorphism analytic strategies comparable to those recently developed for MEN-IIa become available [30].

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