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Family History as a Risk Factor for Ulcerative Colitis–Associated Colon Cancer in Cotton-Top Tamarin

ELIZABETH R. BERTONE,* EDWARD L. GIOVANNUCCI,† NORVAL W. KING, Jr.,§
ANDREW J. PETTO,§ and LORNA D. JOHNSON§

*Departments of Epidemiology and Nutrition, Harvard School of Public Health, Boston; †Department of Medicine, Harvard Medical School, and Department of Nutrition, Harvard School of Public Health, Boston; and §New England Regional Primate Research Center, Harvard Medical School, Boston, Massachusetts

Background & Aims: Little is currently known about the relationship between family history of colon cancer and ulcerative colitis–associated colon cancer. A nested case-control study was performed to evaluate the association between family history of colon cancer and spontaneously occurring colon cancer in cotton-top tamarins (*Saguinus oedipus*). **Methods:** Subjects were chosen from a colony of cotton-top tamarins held in captivity between 1968 and 1995. The cancer status of parents and grandparents was compared for 48 animals with colon cancer and 58 controls, all with histological confirmation of ulcerative colitis. Multivariate odds ratios were calculated using logistic regression. **Results:** A parental history of colon cancer was positively associated with risk of colon cancer (multivariate odds ratio, 2.7; 95% confidence interval, 1.1–6.3). Risk also increased as an animal's total number of family members with colon cancer increased (multivariate odds ratio, 1.7 for each increase in the total number of family members with cancer; 95% confidence interval, 1.1–2.8). **Conclusions:** The results suggest that cotton-top tamarins with ulcerative colitis are at significant increased risk for developing colon cancer if they have a family history of colon cancer. Further investigation of this relationship in both tamarins and humans is warranted.

In human populations, the association between family history of colon cancer and ulcerative colitis (UC)–associated colon cancer has not been explored fully. The cotton-top tamarin (CTT) has been identified as a potentially useful animal model for understanding the genetic and environmental determinants of colon cancer associated with chronic UC^{1–4}; spontaneous colitis and colon cancer in the CTT have been shown to resemble human UC and its associated cancer in some ways.^{1,2,5} Colon cancer and UC are common in adult CTTs held in captivity.^{5,6} Epidemiological investigation of potential risk factors for these outcomes have focused mainly on diet and transmissible agents, and results have been inconclusive.^{6–8} Few epidemiological studies have under-

taken to evaluate family history of colon cancer as a risk factor for UC-associated colon cancer in the CTT,^{9,10} and none has found strong evidence of a hereditary component to the disease.^{10,11} Our study attempts to evaluate the association between family history and UC-associated colon cancer in CTTs, using epidemiological methods consistent with those of human studies.

Materials and Methods

Study Species

The CTT is a small primate indigenous to the forests of Northern Colombia. Endangered in the wild, none has been imported into the United States since 1976. Breeding in captivity has been successful, and there are now several colonies consisting of more than 100 animals.¹²

UC is highly prevalent among CTTs in captivity, and this species also shows a high incidence of spontaneous colon cancer. It is at this point unclear to what extent wild tamarins suffer from UC and colon cancer,¹³ but these conditions have been well documented in captive populations of CTTs.^{5,6,14–17}

Study Population

Subjects were chosen from the population of CTTs held in captivity at the New England Regional Primate Research Center (NERPRC) between the years 1968 and 1995. CTTs were imported from the wild between 1967 and 1976 and were acquired from other colonies in 1977, 1978, 1982, 1985, and 1988. Of these, there were 34 founding pairs who were bred and reared offspring to adulthood (approximately 2 years of age).

Animals born at NERPRC were reared in one of the following four environments: (1) in large cages with parents, older siblings, and birthmates (family reared); (2) in smaller standard tamarin cages with parents and birthmates but no other siblings (parent reared); (3) in the main nursery with other primate infants until weaning at 3–4 months of age and

Abbreviations used in this paper: 95% CI, 95% confidence interval; CTT, cotton-top tamarin; MV OR, multivariate odds ratio; NERPRC, New England Regional Primate Research Center; OR, odds ratio.

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then returned to the CTT colony and housed in groups until maturity (nursery reared); and (4) in an isolation unit from 1 day of age up to 5 years of age (isolation nursery reared). On reaching maturity, animals from all four rearing situations were paired with genetically appropriate mates.

Large cages for families and juveniles raised in nurseries measured $1.5 \times 1.2 \times 0.76$ m. Standard tamarin cages for 2–4 animals measured $0.84 \times 0.65 \times 0.69$ m. Cages were furnished with perches, tree branches, feeding stations, and nesting boxes. Temperature was maintained between 26.6°C and 29.4°C, and humidity was maintained at >50%. Lights were maintained on a 12-hour light/dark cycle, and windows added natural daylight to the adult quarters of the isolation unit.

CTTs reared in the colony were fed a standard diet consisting of commercially produced canned marmoset food (Zu/Preem, Hills Brothers, Topeka, KS) supplemented with wax worms, crickets, oranges, apples, bananas, yogurt, eggs, marshmallows, and vitamins. Infants reared with families and parents were breast-fed; those raised in the two nurseries were fed human infant formula (simulated milk alternative [SMA]; Wyeth Laboratories, Philadelphia, PA). After weaning, the majority of animals were fed the standard diet described above.

Animals were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Outcome Assessment

Colon cancer status was determined by examination of the entire colon at necropsy. The diagnosis of cancer in living animals is difficult because symptoms are often indistinguishable from those of colitis. Colonoscopy and contrast studies of the colon were not regularly used for diagnosis of sick animals in the earlier years of this study. In later years, when diagnosis could be made in living animals, euthanasia was performed to prevent further suffering. Because diagnosis was made after death in most cases or death quickly followed diagnosis, age at death was used as a proxy for age at diagnosis.

Population for Analysis

All animals were older than 2 years. Because our main interest was family history of colon cancer, we excluded cases for whom parental identity and parental cancer experience were not known. Furthermore, to specifically address the relationship between family history and the incidence of UC-associated colon cancer, we excluded cases who did not have histological confirmation of UC on biopsy or necropsy. Finally, to limit confounding by dietary factors, we limited our study to animals who were fed the standard tamarin diet. This left 48 cases for analysis.

Control animals were selected from the population of animals who were found to be free from cancer at death and necropsy. To maximize similarity with cases, potential controls were eligible only if they met the following conditions (1) died after reaching at least 2 years of age, (2) had information on the

cancer status of both parents, (3) were fed a standard diet, and (4) had histological confirmation of UC on biopsy or necropsy. Fifty-eight controls met the eligibility criteria and were included in the analysis.

Exposure Assessment

Information was collected for 106 study subjects on the primary areas of interest: each parent's cancer status and each grandparent's cancer status. In addition, data on the following variables were collected to evaluate and control for confounding: age, sex, birth year, rearing status, colitis detected on biopsy as opposed to only on autopsy, and total number of parents and grandparents for whom cancer status was known.

Statistical Analysis

Data was analyzed with STATA software (STATA statistics package; Stata Corp., College Station, TX). Fisher's Exact Test was used to compare the distribution of case and control subjects over categories of a variable, whereas Student's *t* test was used to compare the difference between means. *P* values reported are two sided.

Logistic regression was performed using the subject's colon cancer status as the outcome and variables measuring family history of colon cancer as exposure variables. This analysis estimates the odds ratio (OR), which compares the odds of being a case and being exposed (e.g., positive family history) with the odds of being a control and being exposed. An OR of 1.0 indicates that there is no association between the exposure variable and the outcome of interest. An OR of >1.0 implies an increased risk for the outcome among subjects with the exposure compared with the reference group (those without the exposure), whereas a value of <1.0 indicates a decreased risk compared with the reference group. Ninety-five percent confidence intervals (95% CIs) were calculated. A 95% CI that excludes the null value of 1.0 is considered statistically significant at the 0.05 level.

Multivariate logistic regression was used to calculate ORs (multivariate odds ratios [MV ORs]) that were adjusted for the effects of all confounding variables included in the model.

Results

Baseline characteristics of the study population are presented in Table 1. The sex and age distribution of cases and controls were similar (*P* for sex = 0.70; *P* for age = 0.81). Although female CTTs did not develop cancer with greater frequency than males, age at diagnosis was earlier in female animals. The mean age at outcome for female animals was found to be 6.2 years compared with 7.7 years for males (*P* = 0.06). Cases were more likely to be born in the later years of the study than controls (*P* = 0.005). A greater percentage of cases were family reared, whereas more controls were raised with parents or in one of the two nurseries (*P* = 0.09). Fewer controls than cases had colitis detected on biopsy as

Table 1. Background Characteristics of Study Subjects

Characteristics	No. of cases (n = 48) (%)	No. of controls (n = 58) (%)	P value ^a
Sex			
Female	27 (56)	35 (60)	0.70
Male	21 (44)	23 (40)	
Age (yr)			
2.0–4.9	13 (27)	19 (33)	0.81
5.0–7.9	21 (44)	20 (34)	
8.0–10.9	9 (19)	12 (21)	
≥11.0	5 (10)	7 (12)	
Birth year			
Before 1980	5 (10)	20 (34)	0.005
Between 1980 and 1985	21 (44)	24 (41)	
After 1986	22 (46)	14 (24)	
Rearing status			
Family	32 (67)	26 (50)	0.085
Parent	7 (15)	15 (26)	
Either nursery	9 (19)	17 (29)	
Colitis detected on biopsy	39 (81)	38 (66)	0.083
Colitis detected only on autopsy	9 (19)	20 (34)	
No. of grandparents known			
0	17 (35)	27 (47)	0.52
2	11 (23)	11 (19)	
4	20 (42)	20 (34)	

^aFisher's Exact Test.

opposed to only on autopsy ($P = 0.08$). These five variables were included as covariates in the regression analysis.

Logistic regression was used to evaluate the effect of family history on risk of colon cancer. Crude and MV ORs for family history variables are shown in Table 2. Animals with a parental history of colon cancer (1 or 2 parents diagnosed with cancer) had a crude OR of 2.4 (95% CI, 1.1–5.3; $P = 0.03$). This may be interpreted as a 2.4-fold increase in risk of cancer compared with subjects with no parental history of colon cancer. When age, sex, birth year, rearing status, and colitis detected on biopsy were included in the multivariate analysis, the risk for animals with parental cancer history increased in magnitude (MV OR, 2.7; 95% CI, 1.1–6.3; $P = 0.03$).

When the number of parents with cancer (0, 1, or 2) was treated as a continuous variable, an adjusted OR of 2.1 for each parent with cancer was produced (95% CI, 1.0–4.1; $P = 0.04$). This indicates that the risk for colon cancer increases as the number of parents afflicted increases from 0 to 1 to 2.

There was some evidence that risk of colon cancer differed by the sex of the affected parent (Table 2). History of colon cancer in a subject's mother was a slightly better predictor of the subject's outcome than father's cancer history (MV OR for maternal history of 2.9 [95% CI, 1.1–7.9] vs. MV OR for paternal history of 1.6 [95% CI, 0.6–3.9]).

The effect of a history of colon cancer in grandparents on an animal's risk of cancer was assessed for all subjects; analysis of grandparents' cancer history was limited to subjects for whom cancer status of all grandparents was known ($n = 40$). Animals whose grandparents had a history of cancer were at increased risk for cancer themselves; risk increased 70% for each grandparent with cancer (MV OR, 1.7; 95% CI, 0.7–3.9; $P = 0.23$).

Risk of colon cancer was significantly associated with the total number of parents and grandparents with a history of cancer. Each single increase in the number of family members with cancer (e.g., 2 family members vs. 1 family member) resulted in a 70% increase in cancer risk (MV OR, 1.7; 95% CI, 1.1–2.8; $P = 0.03$). Therefore, subjects with a history of cancer in 3 or more parents and grandparents had more than six times the risk of cancer as those with no family history.

To further investigate the effect of the subject's birth year on the relationship between family history of colon cancer and cancer incidence, we stratified our data by birth year (before 1980, between 1980 and 1985, and after 1985). In each category, subjects with a parental history of colon cancer showed a 3–5-fold increased risk of developing cancer themselves (results not shown). CIs

Table 2. Crude and MV ORs for the Relationship Between Family History Variables and Development of Colon Cancer

Exposure	No. of cases	No. of controls	Crude OR (95% CI)	MV OR ^a (95% CI)
No family history among parents	17	33	1.0	1.0
Family history among parents	31	25	2.4 (1.1–5.3)	2.7 (1.1–6.3)
No. of parents with cancer (0–2) ^b	48	58	2.1 (1.1–4.0)	2.1 (1.0–4.1)
No maternal history of cancer	30	48	1.0	1.0
Maternal history of cancer	18	10	2.9 (1.2–7.1)	2.9 (1.1–7.9)
No paternal history of cancer	28	40	1.0	1.0
Paternal history of cancer	20	18	1.6 (0.7–3.5)	1.6 (0.6–3.9)
No. of grandparents with cancer (0–4) ^{b,c}	20	20	1.2 (0.6–2.3)	1.7 (0.7–3.9)
No. of family members with cancer ^{b,d}	48	58	1.6 (1.1–2.4)	1.7 (1.1–2.8)

^aAdjusted for age, sex, birth year, rearing status, and colitis detected on biopsy vs. only on autopsy. Maternal and paternal histories were adjusted for the cancer history of the other parent.

^bContinuous variable. Reference group is animals with no family history of colon cancer.

^cAnalysis performed on a subset of the total population.

^dAdjusted for the number of family members known (2, 4, or 6).

were wide because of the small number of subjects in each stratum.

Similarly, the increased risk associated with family history persisted when we stratified by method of colitis detection. Seventy-seven animals had colitis detected on biopsy as opposed to on autopsy alone. The MV OR for parental history of colon cancer in this group was 2.2 (95% CI, 0.9–5.9; $P = 0.10$; results not shown). In animals whose colitis was detected only at autopsy, the MV OR associated with parental history of colon cancer was 11.6 (95% CI, 0.7–202; $P = 0.09$); wide CIs and low power again resulted from the small sample size.

Finally, to address whether our findings could be attributed to the fact that many of our subjects were related, we repeated the analyses on a subgroup of subjects consisting of 1 animal from each family. This prevented the inclusion of siblings, parents, and offspring as subjects in the data set. Nineteen cases and 24 controls were included in the subanalysis. Although the power to distinguish a significant association between family history and UC-associated colon cancer was greatly reduced because of the small sample size, the estimates of effect produced in the subanalysis were similar in magnitude to those of the larger study. CTTs with a history of cancer in 1 or both parents had twice the risk of cancer as those from cancer-free parents (MV OR, 2.2; 95% CI, 0.5–10.4; $P = 0.32$; results not shown).

Discussion

Our results indicate that CTTs with a family history of colon cancer are at increased risk for colon cancer compared with those with cancer-free parents and grandparents. Animals with a parental history of cancer were nearly three times more likely to develop cancer themselves than animals with cancer-free parents. Risk increased with the number of affected first- and second-degree family members. The association between positive family history and colon cancer risk persisted in analyses limited to unrelated subjects, suggesting that an inherited factor, in combination with UC, is a cause of colon cancer in CTTs. These results cannot be attributed to differences between cases and controls in terms of diet, rearing experience, or living conditions.

It is possible that the severity and duration of colitis may have differed between cases and controls, although all subjects showed moderate to marked colitis on biopsy and/or autopsy. These variables are difficult to assess in CTTs because the only indication of disease is diarrhea, which is also a symptom of *Campylobacter* infection, which is prevalent in the colony. Inclusion of a variable differentiating between method of colitis detection in our

regression models had little impact on the family history–colon cancer relationship. Similarly, when we stratified by method of colitis detection, results indicated that animals with a parental history of colon cancer had an increased risk for developing colon cancer whether or not they had colitis detected on biopsy. The association was somewhat stronger in subjects whose disease was detected only during autopsy.

Our study was limited by a relatively small sample size. A greater sample size would allow us to further address the relationship between colon cancer risk and the sex of the diseased family member and to better examine the impact of incremental risk of colon cancer for each additional affected family member. The ability to choose subjects from a larger number of eligible animals would allow us to limit the number of animals from each individual family that were included in our study. Because siblings were included as subjects in the larger analysis, we could not address the effect of sibling cancer history on an individual's risk of colon cancer. From our results, as well as observation of the concentration of colon cancer in some families, we would expect individuals' risk of cancer to increase as their number of siblings with cancer increased.

Idiopathic colitis and colon cancer in the CTT have been shown to resemble human UC and its associated cancer.^{1,2,5} In both species, cancer arises from a flat epithelium and tends to be undifferentiated, infiltrating, and multicentric. In the CTT, it occurs at all ages of life, but a large percent occurs earlier than in humans and is right sided.⁵ Additionally, it is often mucinous or composed of signet rings and is seldom preceded by adenomatous polyps or dysplasia. UC in the CTT is diffuse, involving the cecum, colon, and rectum,¹⁷ whereas UC in the human starts in the rectum and progresses in continuity towards the cecum.¹⁸ The onset of UC in the CTT is predominantly before puberty; 66% of disease in family- and parent-reared animals occurs in the first year of life, and 87% occurs within the first 2 years.⁶

Both the CTT cancer and UC-associated human cancer differ from the more common human spontaneous cancer that occurs in later life and is more often in the left colon or rectum.¹⁹ In the human, UC occurs in approximately 4–6 individuals per 100,000.¹⁸ It is estimated that 30% of patients with colitis will develop cancer, and the UC-associated cancer accounts for 1% of the deaths caused by colon cancer.^{20,21} In the CTT, UC is highly prevalent in captive populations (50%–60%),^{6,17} and the associated cancer accounts for 21%¹⁶ to 35%⁵ of deaths among all adults.

A genetic basis for CTT colon cancer has been suggested by several observations. Colon cancer in CTTs

has been observed throughout the world in colonies with diverse environments and diets, and other species of tamarins and marmosets raised similarly to CTTs do not develop the disease.¹⁴

In a study of 10 colony-born CTTs with colon cancer, 3 animals had parents who also had cancer.⁹ In the remaining 7 animals, there were two sets of siblings. In a 6-year study of a cohort of 176 colony-born CTTs, 14% developed cancer.¹⁰ However, the offspring of parents who had died of cancer were not found to be at increased risk compared with those of unaffected parents, and the coefficient of relationship between two pairs of tamarins who had colon cancer was not greater than random sampling between two pairs in the colony.

In another study of the same colony conducted by Cheverud et al.,¹¹ the heritability estimate for the likelihood of developing colon cancer did not differ significantly from zero (heritability estimate, 17%; SD, 14%). From the studies of this colony, it has been suggested that CTTs are genetically at a high risk for colon cancer, but the magnitude of risk is similar among all animals. However, it is possible that Cheverud et al. were unable to detect a statistically significant heritable component to the disease because potential confounders of the family history-colon cancer relationship, such as history of UC and diet, were not taken into account during analysis. It is unclear to what extent study design, method of analysis, and sample size account for differences between their results and ours.

To our knowledge, the association between family history of colon cancer and development of UC-related colon cancer in humans has only been investigated in one study, which produced estimates of risk very similar to ours. Nuako et al.,²² in a study of 153 case patients and 151 controls, found that patients with UC with a family history of colorectal cancer in first-degree relatives had 2.4 times the risk of cancer as patients without a family history (95% CI, 1.1–5.8). Neither family history of UC nor extent and duration of colitis was responsible for the observed association.

Several studies have estimated the risk of developing colon cancer among patients with UC^{20,23–28}; the cumulative incidence of colon cancer has been found to be as high as 30%–40% after long-term follow-up (25–30 years).²⁰ Established risk factors for developing UC-related colon cancer include young age of onset of UC, large extent of the colon involved, and extended duration of active colitis.^{20,25,28} Treatment with sulfasalazine for an extended period (longer than 3 months) has been shown to reduce risk of developing colon cancer.²⁹ Our findings suggest that heritable factors may influence the risk of developing colon cancer among those diagnosed with UC.

Surveillance of the human UC population for development of colon cancer has presented problems. Questions exist surrounding efficacy, cost, patient compliance with treatment, and the potential benefits of preventive surgery.^{4,24,30,31} Given the findings of our study, family history of colon cancer among patients with UC may be another factor to take into account when making decisions on surveillance strategy.

Epidemiological studies of nonhuman primates have several methodological advantages over those using human subjects. Recall bias, observer biases, and misclassification of exposure are greatly reduced because information on disease history, behavioral variables, and other covariates of interest are collected in a prospective manner by a small number of observers. A complete necropsy can be performed after death to ascertain the presence of chronic illness and to determine the ultimate cause of death. This decreases the frequency with which disease goes undetected and limits misclassification of outcome. When careful pedigrees of all animals are kept, information on disease and exposure histories can be constructed for many generations of animals in one genetic line. Therefore, family history studies can be conducted with limited bias, misclassification, and confounding. Although nonhuman primates are biologically similar to humans in many ways, their natural life spans are a great deal shorter. This, combined with the ability to carefully regulate the animals' environments and control mating, make them highly desirable subjects for studies involving genetics and inheritance patterns.

Large colonies of animals kept for breeding and observational research, such as the CTT colony at NERPRC, offer one of few opportunities to collect prospective data on spontaneously occurring disease and exposure variables in a large number of animals. They are a valuable resource that should be considered in future epidemiological investigations.

In summary, our results suggest that CTTs with a family history of colon cancer are at significant increased risk for developing UC-associated colon cancer. Further study to determine the nature of this inherited component is warranted.

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Address requests for reprints to: Lorna D. Johnson, M.D., New England Regional Primate Research Center, P.O. Box 9102, Southborough, Massachusetts 01771. Fax: (508) 624-8181.

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