Risk of Renal and Colonic Neoplasms and Spontaneous Pneumothorax in the Birt-Hogg-Dubé Syndrome[1]

Berton Zbar,[2] W. Gregory Alvord, Gladys Glenn, Maria Turner, Christian P. Pavlovich, Laura Schmidt, McClellan Walther, Peter Choyke, Gregor Weirich, Stephen M. Hewitt, Paul Duray, Fathia Gabril, Cheryl Greenberg, Maria J. Merino, Jorge Toro, and W. Marston Linehan

Laboratory of Immunobiology [B. Z., J. T.], Data Management Services [W. G. A.], Intramural Research Support Program [L. S.], Science Application International Corporation, National Cancer Institute-Frederick, Frederick, Maryland 21702; Dermatology Branch [M. T.], Laboratory of Pathology [M. J. M., S. M. H., P. D.], Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics [G. G.], and Urologic Oncology Branch [W. M. L., C. P. P., M. W.], Center for Cancer Research, National Cancer Institute, Bethesda, Maryland 20894; Diagnostic Radiology, Clinical Center, NIH, Bethesda, Maryland 20894 [P. C.]; Digestive Diseases Branch, National Institute of Diabetes, and Digestive and Kidney Diseases, NIH, Bethesda, Maryland 20894 [F. G.]; Departments of Pediatrics and Child Health and of Biochemistry and Medical Genetics, University of Manitoba, Winnipeg, Manitoba, Canada [C. G.]; and Technical University Munich, D-81675 Munich, Germany [G. W.]

Abstract

The Birt-Hogg-Dubé syndrome, a genodermatosis characterized by benign tumors of the hair follicle, has been associated with renal and colonic neoplasms and spontaneous pneumothorax, but the risk of developing these disorders is unknown. We identified risk factors for renal tumors and spontaneous pneumothorax in 98 patients affected with the Birt-Hogg-Dubé syndrome, in 13 Birt-Hogg-Dubé haplotype carriers, and in 112 unaffected family members. Development of renal tumors was strongly associated with the Birt-Hogg-Dubé syndrome and age. The odds ratio for renal tumor in BHD-affected family members adjusted for age was 6.9 (95% confidence interval, 1.5–31.6) and ~9.0 for the other risk factors considered. Chromophobe renal carcinoma, an uncommon type of renal cancer, was the predominant type of renal cancer found. Spontaneous pneumothorax was also strongly associated with the Birt-Hogg-Dubé syndrome and age. The odds ratio for pneumothorax in BHD-affected individuals, adjusted for age, was 50.3 (95% confidence interval, 6.4–392), and about 32 times higher adjusting for the other risk variables. Colon cancer and colon polyps were not related to the Birt-Hogg-Dubé syndrome. The Birt-Hogg-Dubé syndrome confers an increased risk for the development of renal tumors and spontaneous pneumothorax. We found no increase in risk for the development of colon polyps or colon carcinomas.

Received 9/7/01; revised 12/26/01; accepted 1/25/02.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Funded in part by the National Cancer Institute, NIH, under contract NO1-CO-56000.
[2] To whom requests for reprints should be addressed, at Laboratory of Immunology, National Cancer Institute-Frederick, Frederick, MD 21702

Introduction

In 1977, Drs. Birt, Hogg, and Dubé described a family whose members were affected with multiple, small, white or skin-colored papules located on the face and neck (1). Skin papules developed after age 30 and were frequently associated with acrochordons (skin tags); the disorder seemed to be inherited as an autosomal dominant trait. Pathological studies of these skin lesions showed disorganization of hair follicle structure with thin, elongated, anastomosing strands of epithelial cells extending from hair follicles, and increased numbers of dermal fibroblasts and mucin located adjacent to the epithelial strands. These benign skin tumors, designated fibrofolliculomas (FFs), were considered to be hamartomas (2).

Subsequently, other families with members affected with multiple fibrofolliculomas were described and this genodermatosis was named the BHD.[3] BHD was reported to be associated with renal tumors, spontaneous pneumothorax, colon polyps, colon carcinomas, lipomas, parathyroid adenomas, and parotid gland oncocytomas (3–12). It was not possible to determine whether the health problems reported to be associated with BHD represented chance occurrences, or whether BHD predisposed to a number of neoplastic and developmental disorders. To define the spectrum of health problems associated with BHD, we recruited patients with BHD from dermatologists throughout the United States and Canada and determined the frequency of associated health problems with particular emphasis on renal and colonic tumors and spontaneous pneumothorax. If BHD predisposed to renal and colonic tumors and spontaneous pneumothorax, we would expect the risk of these health problems to be increased in patients affected with BHD compared with their unaffected siblings.

A precise way to define the risk of health problems associated with an inherited disease is to compare the frequency of health problems in all family members who possess the disease gene (both clinically affected individuals and disease gene carriers) to the frequency of these problems in family members who do not carry the disease gene. We tested whether the inheritance of BHD or the BHD haplotype predisposed to the development of renal or colonic neoplasms or of spontaneous pneumothorax by performing a cross-sectional study of BHD families.

Materials and Methods

Patient Recruitment. We recruited members of families affected with BHD by mailings to members of the American

[3] The abbreviations used are: BHD, Birt-Hogg-Dubé syndrome; CT, computed tomography; OR, odds ratio; BMI, body mass index.

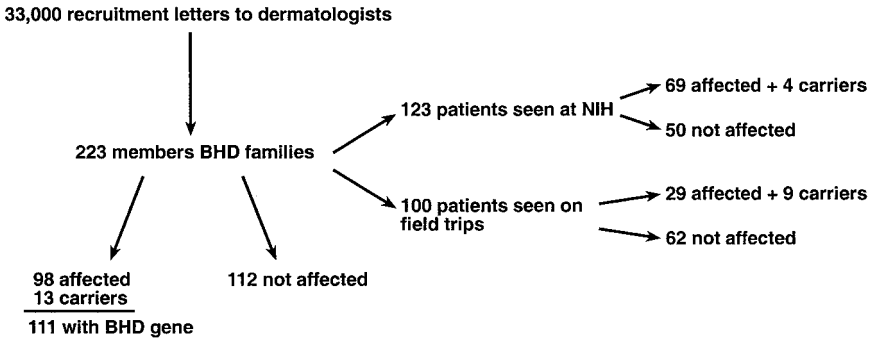

Fig. 1. Scheme of the study.

Academy of Dermatology. About 33,000 patient recruitment letters were sent in three mailings over a 2-year period. We also recruited members of the original family described by Birt, Hogg, and Dubé (1). All of the BHD families were invited to participate in the study regardless of the number of affected individuals in the family or of the presence or absence of associated health problems. Subjects were evaluated in consecutive order with one excluding factor. To avoid overestimating the frequency of renal tumors in BHD, we excluded patients/families referred because of renal tumors who were subsequently found to have BHD, and we also excluded three families with renal tumors and BHD previously seen at the National Cancer Institute (4, 13). We evaluated BHD family members over age 20. The protocol was approved by the Institutional Review Boards of the National Cancer Institute and of the University of Manitoba. All of the members of BHD families who participated in this study gave written informed consent.

Patient Evaluation. Families affected with BHD were evaluated at the Clinical Center, NIH, and also on field trips. Patients were interviewed for a prior history of renal or colonic tumors and spontaneous pneumothorax. Each patient had a detailed examination (by M. T. or J. T.) of the skin including biopsies of lesions suspected to be fibrofolliculomas.

To detect occult renal malignancies, family members who came to the Clinical Center, NIH, were examined by renal ultrasound and abdominal CT scans. To detect occult colonic neoplasms, family members were examined by colonoscopy. To detect parenchymal changes in the lung, family members were examined by high resolution thoracic CT scans. Helical CT was performed through the chest and abdomen using 5-mm collimation. The kidneys were scanned before and after the administration of ~120 ml of Ioxilan 300 (Cook Imaging Corp. Bloomington, IN). High-resolution (1-mm) sections were obtained through the chest at 10-mm intervals. Renal ultrasound was performed with 3–5-Mhz gray scale and color-Doppler transducers with one of two units (Acuson Sequoia, Mountain View, CA, or ATL HDI 8000; Bellevue, WA).

Definitions. We defined an individual as affected with BHD when the individual showed >10 skin lesions clinically compatible with fibrofolliculomas and a minimum of 1 lesion histologically confirmed as a fibrofolliculoma. The pathological diagnosis of fibrofolliculomas required the finding of elongated, anastomosing epithelial strands originating from a hair follicle. We defined a family as affected with BHD when it had one or more members affected with BHD.

We defined a BHD haplotype carrier as an individual who possessed the BHD haplotype but did not possess fibrofolliculomas (below).

Renal tumors were diagnosed on the basis of histological examination of resected tumors or on the basis of CT scans and renal ultrasound. Solid renal lesions >1 cm in diameter with greater than 20 Hounsfield units enhancement were considered renal tumors. Pneumothorax was documented by a review of medical records, by an examination of chest X-rays, and by reviewing the patient's history.

Identification of BHD Haplotype Carriers. Because we wished to determine the frequency of health problems in all of the family members who possessed the BHD gene, we constructed haplotypes based on genotyping results to identify individuals predicted to possess the BHD disease gene but who lacked cutaneous signs of the disease (BHD haplotype carriers). We have recently shown that the BHD gene is located at chromosome 17p11.2 in a 4-cM region between the polymorphic DNA markers D17S1857 and *D17S805* (14). Haplotypes were constructed by examining the inheritance of polymorphic DNA markers located in the BHD gene region to identify alleles that were consistently inherited with the disease phenotype.

Statistical Analysis. Significant univariate associations with renal tumors as the criterion variable were identified using the χ^2 test of independence. Associations for renal cancer and colon polyps were assessed with Fisher's exact test. We report *P*s from likelihood ratio χ^2 statistics because these were identical to those obtained in logistic regression runs with renal tumor and pneumothorax modeled, respectively, as criterion variables. [Pearson χ^2 estimated values were in close agreement with those provided by likelihood ratio criterion and provided identical interpretations.] We report *P*s between 0.05 and 0.10 as marginally significant and those <0.05 as significant. We considered BHD as the primary exposure variable of interest, and age, sex, smoking status, hypertension, BMI and screening status (patients seen on field trips were not examined by CT) as possible confounding risk variables. Variables associated with the development of renal tumors and spontaneous pneumothorax were identified by univariate and multivariate logistic regression (15, 16).

Results

Patient Description. We studied 223 members of 33 Caucasian BHD families (Fig. 1; Table 1). The number of individuals studied per family ranged from 1 to 57. The number of individuals affected with BHD studied per family ranged from 1 to 15. We were able to determine BHD haplotypes in 182 (82%) of 223 individuals (Table 1). In our study, there were 98 BHD affected individuals, 13 BHD haplotype carriers, and 112 non-affected individuals. The characteristics of members of the study are in Table 2. The mean age of the BHD affected group

Table 1 Description of BHD families in the study

Family ID[a]	No. of family members	No. of affected family members	No. of family members with haplotype determined	BHD haplotype carriers no. of patients	Proband with renal cancer	Renal cancer no. of patients	Pneumothorax no. of patients	Colon polyps no. of patients	Colon cancer no. of patients
172	57	15	57	4		1	5	1	
174	29	9	31	2	Yes	3	0	3	1
175	1	1				0	0		
176	1	1				0	1		
182	2	2				0	0	1	
183	1	1			Yes	1	1		
184	2	1				1	0		
185	1	1			Yes	1	1		
188	2	2				0	0		
193	2	2				0	0		
198	4	1				0	0		
200	7	3	6	1		1	2	1	
201	8	5	7	0		0	0	1	
202	20	7	20	3		3	0	2	
207	1	1				0	0	1	
208	3	1				0	0		
209	2	2				0	0		
210	9	5	9	2		0	3		1
211	1	1				0	0		1
213	2	1				1	0		
215	1	1				0	0		
216	7	5	7	0		2	2		
217	1	1				1	1		
224	1	1				0	0		
226	1	1				0	0		
228	20	9	20	1		2	3		
230	17	4	17		Yes	1	2	1	
231	2	2				0	1	1	
232	11	5	8			0	0	3	
233	1	1				0	0		
234	2	2				0	2		
235	3	3				0	1		
236	1	1				0	1		
Totals	223	98	182	13	4	18	26	15	3

[a] ID, identification number.

Table 2 Characteristics of family members affected and not affected with BHD

Variable	BHD		Overall
	Affected	Not affected	
Current age, yr	50.8 (14.1)[a]	43.9 (15.9)	47.3 (15.4)
Male	58 (52%)[b]	57 (51%)	115 (52%)
Female	53 (48%)[b]	55 (49%)	108 (48%)
Hypertension	25 (23%)[b]	18 (16%)	43 (20%)
Smokers (current or previous)	41 (37%)[b]	34 (31%)	75 (34%)
BMI	27.3 (4.9)[c]	26.9 (5.4)	27.1 (5.1)
Seen at NIH	73 (66%)[b]	50 (45%)	123 (55%)

[a] Mean (SD) in years.
[b] *n* (percentage).
[c] Mean (SD) in kg/m^2.

was 50.8 years; the mean age of the BHD not-affected group was 43.9 years. One hundred twenty-three family members were seen at NIH and had abdominal and thoracic CT scans (Fig. 1); 100 family members were seen on field trips and were not examined by CT. The gross and histological characteristics of the skin lesions characteristic of this disorder are shown in Fig. 2, *A* and *B*.

Renal Tumors in BHD Families. There were 18 patients with renal cancer in this series of 223 members of BHD families. Fifteen cases of renal cancer occurred in individuals affected with BHD, 1 case of renal cancer occurred in a BHD-haplotype carrier, and 2 cases of renal cancer occurred in family members not affected with BHD. Individuals with renal cancer were found in 14 of the 33 BHD families. In 10 cases, family members had a history of renal cancer; in 8 cases, renal cancer was detected by screening procedures.

Univariate Analyses: Renal Tumors. Of the 223 subjects investigated, 8.1% had renal tumors. We defined "affected with BHD" by two different sets of criteria in the univariate analyses (Table 3). In the first analysis, we considered both individuals who were clinically affected with BHD and individuals who carried the BHD haplotype as "affected." By this criterion, 14.4% of those affected possessed renal tumors compared with 1.8% not affected ($P = 0.0002$). The odds of developing a renal tumor was 9.3 times greater for persons affected with BHD. In the second analysis, individuals who carried the BHD haplotype (carriers) were considered as not affected. By this criterion, 15.3% of those affected possessed renal tumors compared with 2.4% of those not affected ($P = 0.0003$). In this case, the odds of contracting a renal tumor was 7.3 times as great for those affected with BHD. In subsequent calculations, both

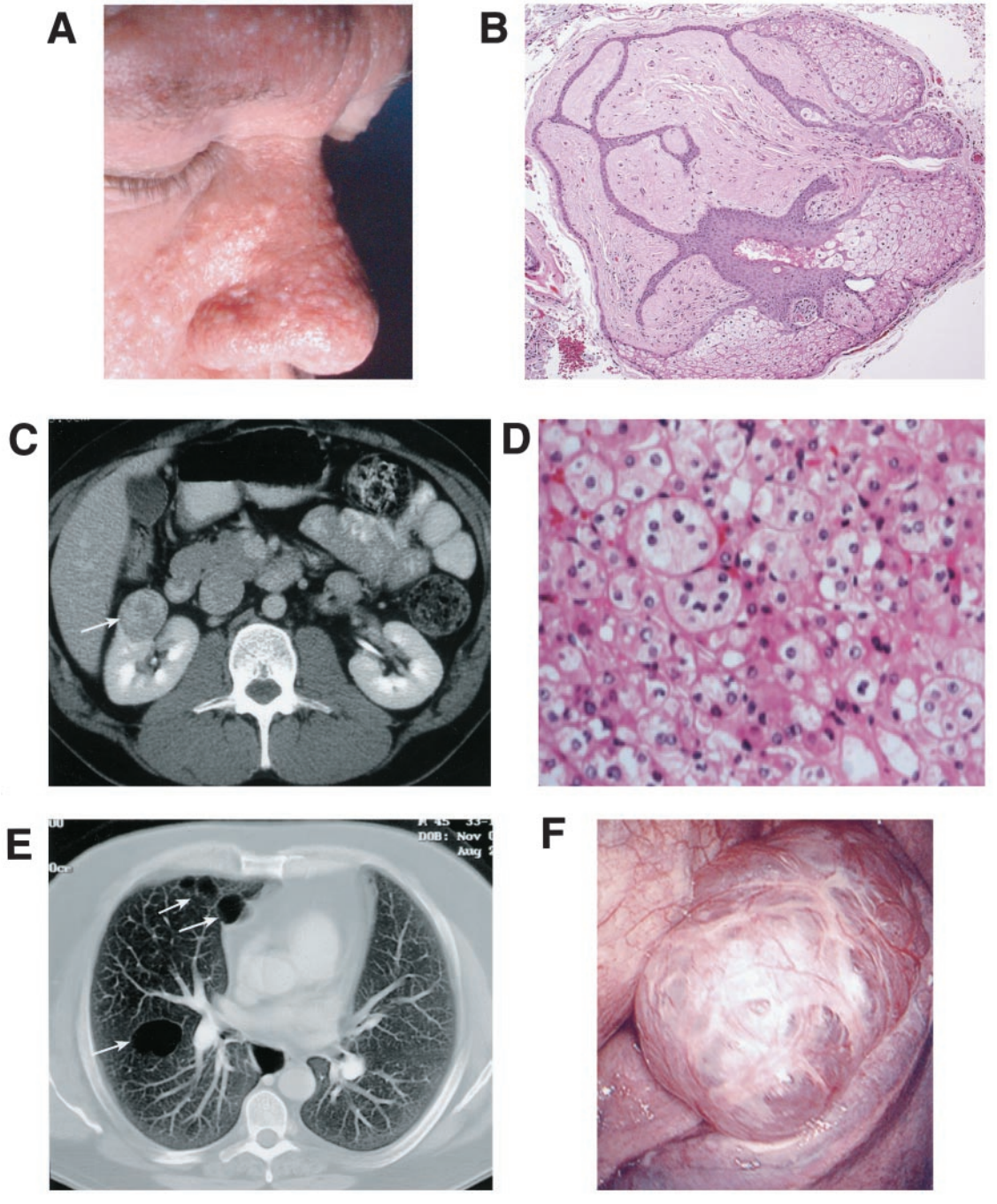

Fig. 2. Clinical manifestations of BHD. *A*, appearance of forehead and nose of a 65-year-old man affected with BHD: numerous shiny, white papules, 2–3 mm in diameter, on the nose and forehead. *B*, photomicrograph of a fibrofolliculoma from a 73-year-old man affected with BHD. The elongated, anastomosing epithelial strands and the dense connective tissue stroma are visible. *C*, abdominal CT scan showing the location of a renal tumor in a 41-year-old man with BHD; the resected neoplasm was a chromophobe renal carcinoma. *D*, photomicrograph of a renal chromophobe renal carcinoma from a patient with BHD; ×200. *E*, thoracic CT showing appearance of lung cysts in a patient with BHD. *F*, appearance of the pleural surface of the left lower lobe from a 46-year-old man with BHD and recurrent spontaneous pneumothorax. Numerous purple blebs on the surface of the lung can be seen. The image was obtained by video-assisted thoracoscopy.

individuals who were clinically affected with BHD and BHD haplotype carriers were considered together.

Age was associated with the development of renal tumors ($P = 0.0054$): 11.9% of patients over 40 years of age developed renal tumors compared with 2.3% younger patients (<41 years). The persons were 5.8 times more likely to develop renal tumors than those in the younger age bracket.

Gender was marginally associated with the development of renal tumors ($P = 0.063$), males being about twice as likely as females to develop tumors. History of hypertension was also

Table 3 Renal tumor according to exposure (BHD) and other potential risk variables (univariate analyses)

Variable	*n*	Renal tumor *n* (%)	OR (95% CI[a])	LR χ *P*
BHD[b]	223	18 (8.1)		
Not affected with BHD	112	2 (1.8)	1	
Affected with BHD	111	16 (14.4)	9.3 (2.1–41.3)	0.0002
BHD[c]	223	18 (8.1)		
Not affected with BHD	125	3 (2.4)	1	
Affected with BHD	98	15 (15.3)	7.3 (2.1–26.2)	0.0003
Age[d]	223	18 (8.1)		
40 yr and younger	88	2 (2.3)	1	
Over 40 yr old	135	16 (11.9)	5.8 (1.3–25.8)	0.0054
Sex	223	18 (8.1)		
Female	108	5 (4.6)	1	
Male	115	13 (11.3)	2.6 (0.9–7.6)	0.063
Smoker	221	18 (8.1)		
No	146	10 (6.8)	1	
Yes[e]	75	8 (10.7)	1.6 (0.6–4.3)	0.33
History of hypertension	220	18 (8.2)		
No	177	11 (6.2)	1	
Yes	43	7 (16.3)	2.9 (1.1–8.1)	0.046
BMI	222	18 (8.1)		
Low (<23.85)	66	3 (4.5)	1	
High (>23.85)	156	15 (9.6)	2.2 (0.6–8.0)	0.18
Site	223	18 (8.1)		
Seen on field trip	100	6 (6.0)	1	
Screened for renal tumors at NIH	123	12 (9.8)	1.7 (0.6–4.7)	0.30

[a] CI, confidence interval; LR, likelihood ratio.
[b] Carriers of BHD included as affected with BHD.
[c] Carriers of BHD not included as affected with BHD.
[d] Age at diagnosis for patients with renal tumors.
[e] Includes smokers and former smokers.

Table 4 Adjusted ORs for development of renal tumor with BHD syndrome taken as the primary exposure variable adjusted for each potential confounding variable (multivariate analysis)

BHD adjusted for each variable	Adjusted OR (95% CI)[c]	LR χ^2 *P*[a]
BHD Adjusted for age		
Not affected with BHD	1	
Affected with BHD	6.9 (1.5–31.6)	0.0025
BHD Adjusted for gender		
Not affected with BHD	1	
Affected with BHD	9.4 (2.1–42.1)	0.0002
BHD Adjusted for smoking status		
Not affected with BHD	1	
Affected with BHD	9.1 (2.0–40.5)	0.0003
BHD Adjusted for hypertension		
Not affected with BHD	1	
Affected with BHD	8.9 (2.0–39.9)	0.0004
BHD Adjusted for BMI		
Not affected with BHD	1	
Affected with BHD	9.1 (2.0–40.5)	0.0003
BHD Adjusted for site		
Not affected with BHD	1	
Affected with BHD	9.0 (2.0–40.5)	0.0004

[a] CI, confidence interval.
[b] LR, likelihood ratio probability associated with the contribution of BHD in the logistic regression equation after adjusting for the variable indicated.

related to the development of renal tumor ($P = 0.046$). Those with a history of hypertension were about 3 times as likely to develop renal tumors as those with no history.

In our study, there was no significant relationship between BMI and renal tumor. Neither smoking status, nor screening showed a significant relationship with renal tumor.

Multivariate Analyses: Renal tumors. We next performed multivariate logistic regression analyses to determine whether age, gender, smoking status, hypertension, BMI, and screening status might act as confounding variables when BHD was considered as the primary exposure variable (Table 4). When BHD was adjusted for age, the OR for a person with BHD developing a renal tumor was 6.9 times that for a person not affected with BHD ($P = 0.0025$). Age was significantly related to the exposure factor (BHD; $P = 0.0001$) and was also significantly related to the criterion variable (renal tumor; $P = 0.0054$) although not a consequence of the exposure factor, BHD. It is, therefore, a confounding risk variable (15, 16).

None of the other potential risk factors qualified as confounding variables. Gender, smoking status, hypertension, and BMI were not related to the exposure variable, BHD. Screening status, although related to BHD, was not significantly related to the criterion variable, renal tumor. For each of these variables taken individually, the odds of BHD-affected individuals for developing renal tumors were about 9 times the odds of those who were not affected (Table 4) and equivalent to the odds for developing renal tumors without adjustment (Table 3).

Pathology of BHD Renal Tumors. We were able to evaluate the pathology of renal tumors in 12 BHD-affected and 2 nonaffected individuals (Fig. 2, *C* and *D*). Renal tumors were multiple in 8 of 12 BHD-affected patients and were multiple and bilateral in 4 of 12 BHD-affected patients. Renal tumors in BHD-affected family members were classified as chromophobe renal carcinoma (seven patients), chromophobe-oncocytic tumor (hybrid tumor, one patient), and clear-cell renal carcinoma (four patients; Refs. 17, 18). Microscopic foci of oncocytosis were seen in the kidneys of 5 of 12 BHD-affected patients. The two nonaffected family members had single clear-cell renal carcinomas. The median age for detection of renal tumors in patients affected with BHD was 51 years.

Spontaneous Pneumothorax in BHD Families. There were 26 patients with spontaneous pneumothorax in this series of 223 members of BHD families. Twenty-one cases of pneumothorax occurred in family members affected with BHD; 4 cases occurred in BHD gene carriers; and 1 case of pneumothorax occurred in a family member not affected with BHD. Because of the small size of this individual's family, we were unable to determine whether this individual was a BHD gene carrier. Cases of pneumothorax occurred in 13 of 33 BHD families.

In some individuals, pneumothorax occurred repeatedly and pneumothorax affected both lungs (Fig. 2, *E* and *F*). Episodes of pneumothorax ceased after surgical intervention. At the time of surgical repair for repeated spontaneous pneumothorax, numerous blebs were seen on the pleural surface (Fig. 2*F*).

Univariate Analyses: Spontaneous Pneumothorax. Of the 223 patients investigated, 11.7% had a history of spontaneous pneumothorax (Table 5). To reiterate, we defined "affected with BHD" by two different sets of criteria in the univariate analyses. In the first analysis, we considered both individuals who were clinically affected with BHD and individuals who carried the BHD haplotype as affected. By this criterion, 22.5% of those affected possessed pneumothorax compared with 0.9% not affected ($P = 0.0001$). The odds of a person developing pneumothorax was 32.3 times greater for persons affected with BHD. In the second analysis, individuals who carried the BHD

Table 5 Pneumothorax according to exposure (BHD) and other potential risk variables (univariate analyses)

Variable	*n*	Pneumothorax *n* (%)	OR (95% CI)[a]	LR χ *P*
BHD[b]	223	26 (11.7)		
Not affected with BHD	112	1 (0.9)	1	
Affected with BHD	111	25 (22.5)	32.3 (4.3–243)	0.0001
BHD[c]	223	26 (11.7)		
Not affected with BHD	125	5 (4.0)	1	
Affected with BHD	98	21 (21.4)	6.5 (2.4–18.1)	0.0001
Age[d]	221	24 (10.9)		
40-yr and Younger	102	18 (17.6)	1	
Over 40 yr old	119	6 (5.0)	0.2 (0.1–0.6)	0.0023
Sex	223	26 (11.7)		
Female	108	14 (13.0)	1	
Male	115	12 (10.4)	0.8 (0.3–1.8)	0.56
Smoker	221	26 (11.7)		
No	146	16 (11.0)	1	
Yes[e]	75	10 (13.3)	1.2 (0.5–2.9)	0.61
History of hypertension	220	26 (11.7)		
No	177	20 (11.3)	1	
Yes	43	6 (14.0)	1.3 (0.5–3.4)	0.63
BMI	222	26 (11.7)		
Low (<23.85)	66	8 (11.5)	1	
High (>23.85)	156	18 (12.1)	0.9 (0.4–2.3)	0.90
Site	223	26 (11.7)		
Seen on field trip	100	9 (9.0)	1	
Seen at NIH	123	17 (13.8)	1.6 (0.7–3.8)	0.26

[a] CI, confidence interval; LR, likelihood ratio.
[b] Carriers of BHD included as affected with BHD.
[c] Carriers of BHD not included as affected with BHD.
[d] Age at diagnosis for patients with pneumothorax.
[e] Includes smokers and former smokers.

haplotype (carriers) were considered as not affected. By this criterion, 21.4% of those affected possessed renal tumors compared with 4.0% not affected ($P = 0.0001$). In this case, the odds of a person having pneumothorax was 6.5 times as great for those affected with BHD.

Age was inversely associated with pneumothorax ($P = 0023$). Only 5.0% of the older patients (>40 years) had pneumothorax compared with 17.6% of younger patients (<41 years). Hence, younger patients were about four times as likely as older patients to have pneumothorax. (The OR is the inverse of the OR of 0.25 reported in Table 4.)

The remaining variables in Table 4, gender, smoking status, history of hypertension, BMI, and screening status, were not related to pneumothorax.

Multivariate Analyses: Spontaneous Pneumothorax. When BHD was adjusted for age, the odds that a person would have pneumothorax was 50.3 times greater than for a person not affected with BHD (Table 6). This finding is because a greater proportion of young people had pneumothorax.

For all other variables (gender, smoking status, hypertension, BMI, and screening status) the adjusted odds were about 32 times as great for those with BHD as for those without (Table 6). These values are comparable with those obtained by the crude OR that was computed for the impact of BHD on pneumothorax without adjusting for potential confounders (Table 5).

Pulmonary Cysts in Patients with BHD. To determine whether there were precursor lesions in the lungs that predisposed to spontaneous pneumothorax, members of BHD families were examined by high-resolution thoracic CT scans. Pulmonary cysts were frequently detected (83%) in affected members of BHD families; pulmonary cysts were identified in 10% of unaffected control members of BHD families ($P = 0.0001$; Fig. 2*E*). Pulmonary cysts were typically well circumscribed and separate from each other. Each cyst was lined by a smooth, definable wall that did not enhance. The majority of cysts were basilar and subpleural, but small intraparenchymal cysts were also seen.

Table 6 Adjusted ORs for development of pneumothorax with BHD taken as the primary exposure variable adjusted for each potential confounding variable (multivariate analysis)

BHD adjusted for each variable	Adjusted OR (95% CI)[a]	LR[b] χ^2 *P*
BHD adjusted for age		
Not affected with BHD	1	
Affected with BHD	50.3 (6.4–392)	0.0001
BHD adjusted for gender		
Not affected with BHD	1	
Affected with BHD	32.6 (4.3–245)	0.0001
BHD adjusted for smoking status		
Not affected with BHD	1	
Affected with BHD	32.2 (4.3–242)	0.0001
BHD adjusted for hypertension		
Not affected with BHD	1	
Affected with BHD	32.7 (4.3–246)	0.0001
BHD adjusted for BMI		
Not affected with BHD	1	
Affected with BHD	32.2 (4.3–243)	0.0001
BHD adjusted for site		
Not affected with BHD	1	
Affected with BHD	32.1 (4.2–244)	0.0001

[a] CI, confidence interval.
[b] Likelihood ratio probability associated with the contribution of BHD in the logistic regression equation after adjusting for the variable indicated.

Frequency, Risk, and Characteristics of Colonic Tumors in Patients with BHD. Of the 223 family members in the study, 3 individuals of the 111 BHD-affected group had colon cancer, whereas none of the 112 non-BHD-affected group had colon cancer. This result was not statistically significant ($P = 0.12$, by Fisher's exact test). There were four deceased BHD family members with colon carcinoma in whom we were unable to determine BHD affection status.

With respect to colon polyps, 83 persons were examined by colonoscopy. Of the 45 BHD-affected persons, 8 had colon polyps (18%). Of the 38 non-BHD-affected family members, 7 had colon polyps (18%). These proportions were not statistically different ($P = 1.00$ by Fisher's exact test).

Discussion

We studied patients affected with BHD to determine whether they were predisposed to develop renal and colonic tumors and/or spontaneous pneumothorax and, if so, to quantify the degree of risk and to describe the characteristics of the associated health problems. In agreement with earlier reports, we found that BHD predisposed to renal tumors and spontaneous pneumothorax. The increased risk of renal cancer in individuals who possessed the BHD gene did not appear to be attributable to the presence of a confounding variable. Age was the only variable that acted as a confounder in our study. It partially accounted for the development of renal tumors. However, even with age taken into account, the odds were still 6.9 times greater for those with BHD to develop renal tumors than for those

without BHD. Adjusting for each of the other variables had no impact on the OR for developing renal tumors.

The biological characteristics of the renal tumors found in BHD patients also provided support for the concept that BHD conferred an inherited predisposition to develop renal tumors. In patients with an inherited predisposition to develop renal cancer, renal tumors are usually multiple and bilateral; numerous microscopic renal tumor precursors may be observed within the normal renal parenchyma (19–22). Individuals with a particular type of inherited susceptibility to renal cancer may all be affected with an uncommon histological type of renal cancer (21). Renal tumors in BHD patients were multiple in 8 of 12 patients and multiple and bilateral in 4 of 12 patients. Some BHD patients with renal tumors had foci of oncocytosis (18). Chromophobe renal carcinoma, an uncommon histological type of renal cancer, was the predominant type of renal tumor found in BHD patients (17). A comprehensive evaluation of the pathology of the renal tumors found in BHD patients is in progress.[4]

Thoenes *et al.* (17) identified a histologically distinct form of renal carcinoma that they designated "chromophobe." They found two morphological variants of this tumor. Characteristic pathological features of chromophobe renal carcinomas were the presence of cytoplasmic microvesicles and the expression of cytokeratins but not of vimentin. Patients with chromophobe renal carcinoma appeared to have a better prognosis than patients with clear-cell renal carcinoma.

Spontaneous pneumothorax was a prominent feature of BHD. The strong association of spontaneous pneumothorax with BHD suggests that the presence of spontaneous pneumothorax in a member of a BHD family could be used as a criterion for the diagnosis of BHD. Families have been described with hereditary spontaneous pneumothorax as their major health problem (23, 24). In some families, the predisposition to pneumothorax was inherited as an autosomal dominant trait. Germ-line mutations in the BHD gene may cause some cases of inherited spontaneous pneumothorax.

Early reports from Germany suggested that BHD was associated with a predisposition to colon neoplasms (7–9). This putative association was named the Knickenberg-Hornstein syndrome. In our series, we found that colonic neoplasms were not associated with BHD.

In this study of health problems associated with an inherited illness, we used unaffected family members as controls. This study design has the advantage of producing a control population closely matched to the test population in age, gender, genetic background, and environmental exposure. With this study design, comparisons can be drawn between family members with and without the mutant gene. A disadvantage of this test design is the possible presence of disease gene carriers (susceptibles) in the control group (25). Disease gene carriers who lack the diagnostic features of the inherited illness might nevertheless have some manifestations of the disorder. Indeed, we found obligate gene carriers (clinically unaffected parents of affected children) with spontaneous pneumothorax. We also found other "skin negative" family members with a history of pneumothorax. To correct the problem associated with our study design, we identified family members who inherited the BHD haplotype (the chromosomal segment bearing the disease gene) and, for risk determination, analyzed them together with the BHD-affected group.

One limitation of the present study is that we were not able to screen the entire population studied, and that fewer controls were screened than affected. Of the 111 BHD affected individuals, 71 (65%) were screened by abdominal CT scan; of the 112 unaffected control individuals, 50 (45%) were screened by abdominal CT scan. The failure to screen the entire affected population for renal tumors would lead to an underestimation of risk. The failure to screen the entire unaffected control population for renal tumors raises the possibility of overestimating the risk. However, the frequency of renal tumors detected by CT and ultrasound in our control group (0 of 50) are consistent with the results of a study of 219,640 Japanese by abdominal ultrasound examination. Renal carcinomas were detected by abdominal ultrasound at a frequency of 1 (0.09%) of 1144 patients examined (26, 27). As noted above, whether patients were screened by CT was not found to be a confounding variable.

BHD needs to be considered in the differential diagnosis in any patient with renal cancer, particularly in patients with chromophobe renal carcinomas, and/or patients with multiple or bilateral renal carcinomas. BHD also needs to be considered in the differential diagnosis in any patient with spontaneous pneumothorax, particularly when there is a family history of pneumothorax. It is important to emphasize that in some patients, spontaneous pneumothorax and renal tumors occurred in the absence of cutaneous manifestations of the syndrome. Although in some patients affected with BHD, there were numerous characteristic skin lesions, in other patients there were few characteristic skin lesions, and the diagnosis was more difficult to establish. Once the BHD gene is identified, it will be possible to determine the role of germ-line BHD mutations in BHD and in clinically overlapping disorders, and to determine the contribution of somatic mutations in the BHD gene to the pathogenesis of sporadic renal carcinomas.

Acknowledgments

We thank Dr. Mahul Amin and Dr. Victor Reuter for consultations on renal tumor pathology, Dr. Shane Silver for assistance in studying Family 172, and Cia Manolatos, Robin Eyler, Arlene Berman, Kathy Hurley, James Peterson and Lindsay Middelton for their many contributions to this project. We thank Dr. Wong-Ho Chow for helpful discussions.

References

1. Birt, A. R., Hogg, G. R., and Dubé, W. J. Hereditary multiple fibrofolliculomas with trichodiscomas and acrochordons. Arch. Dermatol., *113:* 1674–1677, 1977.

2. Ackerman, A. B., de Viragh, P. A., and Chongchitmant, N. Neoplasms with Follicular Differentiation, pp. 245–278. Philadelphia: Lea and Febiger, 1993.

3. Roth, J. S., Rabinowitz, A. D., Benson, M., and Grossman, M. E. Bilateral renal cell carcinoma in the Birt-Hogg-Dubé syndrome. J. Am. Acad. Dermatol., *29:* 1055–1056, 1993.

4. Toro, J., Glenn, G., Duray, P., Darling, T., Weirich, G., Zbar, B., Linehan, W. M., and Turner, M. Birt-Hogg-Dubé syndrome: a novel marker of kidney neoplasia. Arch. Dermatol., *135:* 1195–1202, 1999.

5. Binet, O., Robin, J., Vicart, M., Ventura, G., and Beltzer-Garelly, E. Fibromes perifolliculaires polypose colique familaile pneumothorax spontanes familiaux. Ann. Dermatol. Venereol., *113:* 928–930, 1986.

6. Hornstein, O. P. Generalized dermal perifollicular fibroma with polyps of the colon. Hum. Genet., *33:* 193–197, 1976.

7. Hornstein, O. P., and Knickenberg, M. Perifollicular fibromatosis cutis with polyps of the colon—a cutaneo-intestinal syndrome *sui generis*. Arch. Dermatol. Res. *253:* 161–175, 1975.

8. Le Guyadec, T., Dufau, J-P., Poulain, J-F., Vaylet, F., Frossin, M., and Lanternier, G. Trichodiscomes multiples associes a une polypose colique. Ann. Dermatol. Venereol. *125:* 717–719, 1998.

9. Schachtsschabel, A. A., Kuster, W., and Happle, R. Perifollikulare fibrome der haut und kolonpolypen: Hornstein-Knickenberg syndrom. Hautarzt, 47: 304–306, 1996.

[4] C. Pavlovitch. Renal tumors in the Birt-Hogg-Dubé syndrome, manuscript in preparation.

10. Rongioletti, F., Hazini, R., Gianotti, G., and Rebora, A. Fibrofolliculomas, trichdiscomes and acrochordons (Birt-Hogg-Dubé) associated with intestinal polyposis. Clin. Exp. Dermatol., *14:* 72–74, 1989.

11. Chung, J. Y., Ramos-Caro, F. A., Ford, M. J., and Flowers, F. Multiple lipomas, angiolipomas, and parathyroid adenomas in a patient with Birt-Hogg-Dubé syndrome. Int. J. Dermatol., *35:* 365–367, 1989.

12. Liu, V., Kwan, T., and Page, E. H. Parotid oncocytoma in the Birt-Hogg-Dubé syndrome. J. Am. Acad. Dermatol., *43:* 1120–1123, 2000.

13. Weirich, G., Glenn, G., Junker, K., Merino, M., Storkel, S., Lubensky, I., Choyke, P., Pack, S., Amin, M., Walther, M. M., Linehan, W. M., and Zbar, B. Familial renal oncocytoma: clinicopathological study of 5 families. J. Urol., *160:* 335–340, 1998.

14. Schmidt, L., Warren, M., Nickerson, M. L., Weirich, G., Matrosova, V., Toro, J. R., Turner, M. L., Duray, P., Merino, M., Hewitt, S., Pavlovitch, C. P., Glenn, G., Greenberg, C., Linehan, W. M., and Zbar, B. Birt-Hogg-Dubé syndrome, a genodermatosis associated with spontaneous pneumothorax and kidney neoplasia, maps to chromosome 17p11.2. Am. J. Hum. Genet., *69:* 876–882, 2001.

15. Collett, D. Modeling Binary Data. London: Chapman and Hall, 1991.

16. Breslow, N. E., and Day, N. E. Statistical Methods in Cancer Research, Vol, 1, IARC Sci. Publ. No. 32. Lyon, France: IARC, 1980.

17. Thoenes, W., Störkel, S. T., Rumpelt, H-J., Moll, R., Baum, H. P., and Werner, S. Chromophobe renal carcinoma and its variants—a report of 32 cases. J. Pathol., *155:* 277–287, 1988.

18. Tickoo, S. K., Reuter, V. E., Amin, M. B., Srigley, J. R., Epstein, J. I., Min, K-W., Rubin, M. S., and Ro, J. Y. Renal oncocytosis. A morphologic study of fourteen cases. Am. J. Surg. Pathol., *23:* 1094–1101, 1999.

19. Walther, M. M., Lubensky, I. A., Venzon, D., Zbar, B., and Linehan, W. M. Prevalence of microscopic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma and no renal disease: clinical implications. J. Urol., *154:* 2010–2014, 1995.

20. Ornstein, D. K., Lubensky, I. A., Venzon, D., Zbar, B., Linehan, W. M., and Walther, M. M. Prevalence of microscopic tumors in normal appearing renal parenchyma of patients with hereditary papillary renal cancer. J. Urol., *163:* 431–433, 2000.

21. Zbar, B., and Lerman, M. I. Inherited carcinomas of the kidney. Adv. Cancer Res., *75:* 164–201, 1998.

22. Lubensky, I. A., Schmidt, L., Zhuang, Z. P., Weirich, G., Pack, S., Zambrano, N., Walther, M. M., Choyke, P., Linehan, W. M., and Zbar, B. Hereditary and sporadic papillary renal carcinomas with c-*MET* mutations share a distinct morphologic phenotype. Am. J. Pathol., *155:* 517–526, 1999.

23. Abolnik, I. Z., Lossos, I. S., Zlotogora, J., and Brauer, R. On the inheritance of primary spontaneous pneumothorax. Am. J. Med. Genet., *40:* 155–158, 1999.

24. Morrison, P. J., Lowry, R. C., and Nevin, N. C. Familial primary spontaneous pneumothorax consistent with true autosomal dominant inheritance. Thorax, *53:* 151–152, 1998.

25. Peto, J. Genetic predisposition to cancer. *In:* J. Cairns, J. L. Lyon, and M. Skolnick (eds.), Banbury Report 4. Cancer Incidence in Defined Populations, pp. 203–213. New York: Cold Spring Harbor, 1980.

26. Mihara, S., Kuroda, K., Yoshioka, R., and Koyama, W. Early detection of renal cell carcinoma by ultrasonographic screening—based on the results of 13 years screening in Japan. Ultrasound Med. Biol., *25:* 1033–1039, 1999.

27. Mitchell, T. L., Pippin, J. J., Devers, S. M., Kimball, T. E., Gibbons, L. W., Cooper, L. L., Gonzalez-Dunn, V., and Cooper, K. H. Incidental detection of preclinical renal tumors with electron beam computed tomography: report of 26 consecutive operated patients. J. Comput. Assisted Tomogr., *24:* 843–845, 2000.