Genetic Epidemiology 17:1–15 (1999)

Increased Cancer Risk Among Relatives of Nonsmoking Lung Cancer Cases

Ann G. Schwartz,[1]* Michael Rothrock,[1] Ping Yang,[2] and G. Marie Swanson[3]

[1]Department of Human Genetics, MCP Hahnemann School of Medicine, Allegheny University of the Health Sciences, Pittsburgh, Pennsylvania
[2]Section of Clinical Epidemiology, Mayo Clinic, Rochester, Minnesota
[3]Cancer Center and College of Human Medicine, Michigan State University, East Lansing

Lung cancer has been shown to aggregate in families of nonsmoking lung cancer cases with an earlier age at onset. The current study evaluates whether relatives of nonsmoking lung cancer cases are at increased risk of cancers at sites other than lung. Families were identified through 257 population-based, nonsmoking lung cancer cases and 277 population-based, nonsmoking controls residing in metropolitan Detroit. Data were collected for 2,252 relatives of cases and 2,408 relatives of controls. First-degree relatives of nonsmoking lung cancer cases were at 1.52-fold (95% CI, 1.02–2.27) increased risk of cancer of the digestive system after adjustment for each relative's age, race, sex, and smoking status. Relative risk estimates also were elevated, but not significantly, for tobacco-related cancers (RR = 1.39) and breast cancer (RR = 1.72). Among first-degree relatives of younger probands (age 40–59), risk was non-significantly increased 72% (95% CI 0.95–3.10) for all cancers combined and 3.14-fold for cancers of the digestive system (95% CI 0.76–12.9). Nonsmoking relatives of cases were at increased risk of all cancer sites combined (RR = 1.32; 95% CI 1.003–1.73), cancers other than lung (RR = 1.37; 95% CI 1.03–1.82), and digestive system cancers (RR = 2.01; 95% CI 1.20–3.37). These findings of moderate familial aggregation for cancers of the lung, digestive system, breast, and tobacco-related sites suggest that common susceptibility genes may act to increase risk for a variety of cancers in families. Genet. Epidemiol. 17:1–15, 1999.

*Correspondence to: Dr. Ann G. Schwartz, Division of Epidemiology, Karmanos Cancer Institute, 110 E. Warren Ave., Detroit, MI 48201.

Received 24 February 1998; Revised 18 August 1998; Accepted 5 September 1998

Contract grant sponsor: National Cancer Institute; Contract grant numbers: R29-CA50383, RO1-CA60691; Contract grant sponsor: Institute of Occupational Safety and Health; Contract grant number: RO1-OH02067; Contract grant sponsor: National Cancer Institute; Contract grant number: NO1-CN05225.

Key words: lung cancer; familial aggregation; tobacco exposure

INTRODUCTION

Studies of site-specific familial aggregation of cancer have provided important leads in understanding the genetics underlying cancer development. Familial aggregation demonstrated both in rare cancers, such as bilateral retinoblastoma, and in more common cancers, such as breast and colon, has lead to the identification of cancer genes (e.g., *RB1, BRCA2, APC*) [Cavenee et al., 1986; Wooster et al., 1995; Olschwang et al., 1993]. Site-specific familial aggregation of lung cancer, consistent with Mendelian inheritance patterns, also has been reported. Ooi et al. [1986] showed a 2.4-fold excess of lung cancer among first-degree relatives of lung cancer cases as compared with relatives of spouse controls. Familial aggregation in these families was consistent with a codominant mode of inheritance [Sellers et al., 1990; Gauderman et al., 1997]. Schwartz et al. [1996] has shown a 6-fold increased risk of lung cancer among relatives of nonsmoking lung cancer cases aged 40–59 years after adjustment for individual risk factors. Mendelian codominant inheritance best explained cancer occurrence in the families of these younger nonsmoking probands [Yang et al., in press]. These findings strongly suggest that one or more genes may be inherited in a subset of families leading to increased risk of lung cancer.

Cancers of different sites also aggregate in families, such as in Li-Fraumeni syndrome and breast and ovarian cancer [Li and Fraumeni, 1996; Ford et al., 1994]. Some family clusters of cancer have been well-defined, to the point where successful linkages have been made with particular genetic loci (e.g., *p53, BRCA1*) [Malkin et al., 1990; Miki et al., 1994]. While shared genetic defects explain some family clusters, shared environments, high frequency/low penetrant susceptibility genes, and gene-environment interactions also may be operating. In relatives of smoking lung cancer cases, excess risk of all cancers combined and cancers of the lip, nasal cavity/sinus, mid-ear and larynx, colon, skin, and female reproductive organs has been reported [Sellers et al., 1987, 1991; Shaw et al., 1991; Goldgar et al., 1994]. It has been difficult to determine whether familial aggregation of smoking habits accounts for the aggregation of cancers because most studies include few nonsmokers and do not include risk factor data for relatives. The current study evaluates whether relatives of nonsmoking lung cancer cases are at increased risk of cancers at sites other than lung. This study extends published work by focusing on relatives of nonsmoking probands while considering exposures among relatives in the determination of cancer risk.

MATERIALS AND METHODS

Study Population

The study design has been described in detail elsewhere [Schwartz et al., 1996]. Briefly, eligible cases included 401 population-based lung cancer cases age 40–84 years, newly diagnosed November 1, 1984 through June 30, 1987, who identified themselves as lifetime nonsmokers in a previous study [Swanson et al., 1985; Illis et al., 1987]. These cases were identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS), a participant in the National Cancer Institute's SEER

program. All lifetime nonsmokers among 5,953 lung cancer cases participating in the original study were eligible for the family study. Nonsmokers were defined as anyone not smoking more than 100 cigarettes in their lifetimes. Controls were selected from among the nonsmoking control participants, identified by random digit dialing, in the previous study. Of the 1,429 nonsmoking controls participating, 398 were randomly selected with frequency matching by age within 5-year age group, race, sex, and county of residence. Eligibility was further restricted by excluding cigar and pipe smokers resulting in 314 eligible cases and 345 eligible controls.

Data Collection

For the family study, cases, controls or their proxies were re-contacted. Interviews were conducted by telephone for 257 (81.9%) of the eligible cases and 277 (80.3%) of the eligible controls. Subjects or proxies for interview could not be located for 11.5 and 5.8% of the cases and controls, respectively. Additionally, 6.7% of the cases and 13.9% of the controls refused to participate. Due to the high case fatality associated with lung cancer and the retrospective nature of subject identification, 83% of the case family interviews and 22% of the control family interviews were conducted with proxies. Approximately 84% of the proxies completing interviews were either spouses (27%), siblings (15%), offspring (42%), or parents (0.4%). More than one individual was interviewed to obtain complete information for 24.0 and 6.5% of the case and control subjects, respectively.

The subject questionnaire included a health history, smoking history (number of years and packs per day), environmental tobacco smoke exposure at home and at work (number of hours per day exposed and number of years), and occupational history. For each first-degree relative (parents, siblings, children) and spouse of the cases and controls, age, sex, race, birth year, health history, cancer status, vital status, age at death, cause of death, smoking history, environmental tobacco smoke exposure history, and usual occupation and industry were obtained. Cancers reported among family members were coded using ICD-9 codes. Questionnaire data for 2,252 family members of nonsmoking cases (8.8 per case) and 2,408 family members of nonsmoking controls (8.7 per control) were included.

Analysis

Unconditional logistic regression was used to determine whether cases were more likely than controls to report a first-degree relative with cancer. Models, with case/control status as the outcome, included the following variables: family size (number of relatives, as a continuous measure), age (as a continuous variable), race, and sex of the subjects. Odds ratios (OR) and 95% confidence intervals (CI) were calculated from the regression coefficients in the logistic model.

To determine whether familial risk of cancer was present after taking into account risk factors among the relatives, a cohort approach was taken where cancer status among first-degree relatives was used as the outcome in unconditional logistic regression models with adjustment for correlated data using generalized estimating equation techniques [Zeger and Liang, 1986]. In these models, the family history variable was defined by specifying whether the individual was related to a case or a control. Cases and controls were excluded from this analysis. The following variables were incorporated into all models: age at diagnosis for individuals with cancer

and age at interview or death for unaffected individuals (as a continuous variable), race (dichotomized as African-American and white), sex, family history indicator (relative of a case or of a control), and cigarette smoking history (ever/never). The inclusion of pack-years of smoking, usual occupation and industry, history of other medical conditions, pipe and cigar smoking history, and exposure to environmental tobacco smoke did not appreciably alter the risk estimates associated with family history and are not presented. Individuals with missing data were excluded from the models. Analyses were completed only for those cancer types with at least five control relatives affected. Relative risk estimates (RR) and 95% confidence intervals were calculated from the regression coefficients in the logistic models. Separate models were constructed after stratification by age of the proband and smoking status of the relative. Cumulative incidence of cancer among relatives was determined using Kaplan-Meier product-limit estimators. All statistical analyses were conducted using SAS [SAS Institute, 1990, 1997].

RESULTS

Characteristics of the cases and controls are presented in Table I. The mean age of both the cases and controls interviewed was 69 years. Approximately 20% of both cases and controls were African American. Females accounted for 72% of the cases and 64% of the controls (χ^2 test, $P = 0.06$). This gender difference arose after the exclusion of cigar and pipe smokers from the analysis. Overall, 56.8% of the cases reported a history of cancer in at least one first-degree relative, compared with 49.8% of the controls. Risk of lung cancer in a nonsmoker increased with the number of cancers reported among first-degree relatives (χ^2 test for trend, $P = 0.066$; Table II). The characteristics of the family members are presented in Table III. Mean ages of first-degree relatives were 57.5 and 56.6 years for cases and controls, respectively. The ages of cancer diagnosis by site and for all sites combined were not different for relatives of cases as compared with relatives of controls (*t*-tests, $P > 0.05$ for all comparisons).

Relatives of cases were 20% more likely to develop cancer than relatives of

TABLE I. Characteristics of the Nonsmoking Probands (Lung Cancer Cases and Controls), Metropolitan Detroit, 1984–1987

	Cases (N = 257)		Controls (N = 227)	
Proband characteristics	N	%	N	%
Age group (years)				
40–49	11	4.3	10	3.6
50–59	36	14.0	40	14.4
60–69	70	27.2	85	30.7
70–79	98	38.1	92	33.3
80+	42	16.3	50	18.1
Race				
White	201	78.2	224	80.9
Black	56	21.8	53	19.1
Sex				
Male	72	28.0	99	35.7
Female	185	72.0	178	64.3

TABLE II. Risk Estimates Associated With a First-Degree Family History of Cancer Among Nonsmoking Probands, Metropolitan Detroit, 1984–1987*

Number of cancers among first-degree relatives	Case families (n = 257)	Control families (n = 277)	OR[a]	95% CI
0 cancers	109	137	1.00	
1 cancer	84	83	1.27	(0.85–1.90)
2 cancers	38	37	1.38	(0.80–2.38)
3 + cancers	24	18	1.75	(0.88–3.48)
Unknown	2	2		

*χ^2 test for trend, $P = 0.066$.
[a]Adjusted for age, race, and sex of the proband and family size.

controls (RR = 1.19; 95% CI 0.94–1.50; Table IV). A similar excess risk of cancer was seen for all sites excluding lung cancer (RR = 1.19, 95% CI 0.94–1.51). Risk among first-degree relatives of cases was approximately 1.4-fold or higher than that of relatives of controls for cancers of the digestive system (RR = 1.52), breast (RR = 1.72), and tobacco-related sites (RR = 1.42). Only the RR for cancers of the digestive system reached statistical significance. This excess was seen for both cancers of the esophagus and stomach (RR = 1.67; 95% CI 0.82–3.41) and for colorectal cancers (RR = 1.68; 95% CI 0.93–3.04). Cumulative incidence of cancer for all sites combined and for cancers of the digestive system, breast, and tobacco-related sites was higher across most age groups in relatives of cases as compared with relatives of controls (Fig. 1).

Those at highest risk were the relatives of cases diagnosed before age 60 years (Table V). Although not statistically significant, RRs were higher among relatives of the younger probands for each of the cancer sites presented with the exception of female reproductive system cancers. Among relatives of younger cases, all RRs were greater than 1.4, with highest risk seen for cancers of the digestive system (RR = 3.14; 95% CI 0.76–12.9). All of the risk estimates associated with family history for relatives of probands age 60 to 84 years were 1.6 or lower. As seen for relatives of the younger probands, the highest risk was observed for cancers of the digestive system (RR = 1.42; 95% CI 0.93–2.17).

Differences in cancer risks also were observed between ever and never smoking relatives (Table VI). Among smoking relatives of cases, non-significant risks were

TABLE III. Characteristics of the Family Members of Nonsmoking Probands (Lung Cancer Cases and Controls), Metropolitan Detroit, 1984–1987

	Case families				Control families			
Family member	N	Mean ages	Number with cancer (%)	Mean age at diagnosis	N	Mean ages	Number with cancer (%)	Mean age at diagnosis
All family members	2252	58.7	280 (12.5)	63.2	2408	57.5	274 (11.4)	61.7
Spouses	225	68.7	38 (16.9)	65.7	243	65.1	51 (21.1)	62.4
First-degree relatives	2027	57.5	242 (11.9)	62.7	2165	56.5	223 (10.3)	61.5
Mothers	253	72.5	48 (19.0)	71.8	272	73.3	46 (16.9)	66.0
Fathers	253	70.6	30 (11.9)	71.3	272	71.3	44 (16.2)	70.1
Siblings	900	60.9	133 (14.8)	61.8	936	60.0	115 (12.3)	60.1
Offspring	621	43.1	31 (5.0)	44.9	685	40.7	18 (2.6)	40.5

TABLE IV. Risk Estimates for Cancer Among First-Degree Relatives of Nonsmoking Probands, Metropolitan Detroit, 1984–1987

	Cancer in relatives of cases		Cancer in relatives of controls			
Cancer site	Yes	No	Yes	No	RR[a]	95% CI
All cancers	227	1,622	211	1,828	1.19	(0.94–1.50)
Cancers other than lung	196	1,653	182	1,857	1.19	(0.94–1.51)
Tobacco-associated sites[b]	52	1,797	40	1,999	1.42	(0.90–2.22)
Oral cavity and pharynx	8	1,841	4	2,035	—[c]	
Digestive system	72	1,777	51	2,988	1.52	(1.02–2.27)
Respiratory system	32	1,817	31	2,008	1.12	(0.65–1.93)
Female breast	28	879	19	1,013	1.72	(0.93–3.18)
Uterus	14	893	15	1,017	1.09	(0.49–2.40)
Ovary	7	900	8	1,024	0.94	(0.30–2.92)
Prostate	12	930	13	994	1.00	(0.45–2.23)
Urinary bladder	7	1,842	3	2,036	—[c]	
Kidney	4	1,845	2	2,037	—[c]	
Lymphoreticular system	11	1,838	10	2,029	1.19	(0.51–2.76)
Bone	5	1,844	7	2,032	0.77	(0.25–2.39)
Other/unknown type	38	1,811	54	1,985	0.78	(0.51–1.19)

[a]Adjusted for age, race, sex, and smoking status (ever/never).
[b]Includes cancers of the respiratory system, oral cavity and pharynx, esophagus, urinary bladder, and kidney.
[c]Too few cancers for analysis.

seen for tobacco-related cancers (RR = 1.61; 95% CI 0.91–2.83) and cancers of the respiratory system (RR = 1.36; 95% CI 0.69–2.68), as well as for prostate cancer (RR = 2.23; 95% CI 0.66–7.52). Among never-smokers, case relatives were significantly more likely than control relatives to report cancers of all sites combined (RR = 1.32; 95% CI 1.003–1.73), cancers other than lung (RR = 1.37; 95% CI 1.03–1.82), and digestive system cancers (RR = 2.01; 95% CI 1.20–3.37). A non-significant 1.71-fold increased risk was also observed for breast cancer (95% CI 0.85–3.44).

DISCUSSION

The demonstration of familial aggregation has been used to classify a disease as having an inherited component. We have previously demonstrated familial aggregation of lung cancer in a subset of families of younger onset, nonsmoking lung cancer cases [Schwartz et al., 1996] consistent with Mendelian codominant inheritance [Yang et al., in press]. This study provides evidence that susceptibility to cancer among relatives of nonsmoking lung cancer cases is not limited to cancers of the lung. When cancer risk among relatives was evaluated after adjusting for individual exposures, a positive family history of a nonsmoking lung cancer (being related to a case rather than to a control) was a predictor of cancer development. This was particularly true among relatives of younger probands and among nonsmoking relatives. The most prevalent cancers in these families include cancers of the digestive tract, breast, and those related to tobacco exposure. These results support the hypothesis of an inherited component to risk, with highest familial risk when there is an early onset proband. Also, increased risk for all cancers combined in the absence of a major risk factor (among nonsmoking relatives) suggests a highly susceptible subgroup.

A number of studies have demonstrated a familial component to cancer risk at multiple sites [Sellers et al., 1987, 1991, 1994, 1988; Shaw et al., 1991; Goldgar et al., 1994; Nelson et al., 1993; Schwartz et al., 1988; Anderson et al., 1997]. In the only other reported study that used risk factor data for relatives, excesses for cancers of the nasal/cavity, mid-ear and larynx (OR = 4.6), trachea, lung and bronchus (OR = 3.0), skin (OR = 2.8), and uterus, placenta, ovary and other female organs (OR = 2.1) were reported among relatives of lung cancer cases [Sellers et al., 1987]. Aggregation of smoking-associated cancers in these case families was consistent with Mendelian inheritance [Sellers et al., 1994]. In studying the Utah Mormon population, Goldgar et al. [1994] report increased risk among relatives of lung cancer cases for cancers of the lip (RR = 1.65), cervix (RR = 1.56), and colon (RR = 1.25). Although no adjustments for individual risk factors were made, the Mormon population includes individuals less likely to smoke and, therefore, similar to the nonsmoking probands in the study presented. In the only other study of cancer risk specifically among nonsmokers, Wu et al. [1996] found familial aggregation of lung cancer only. That study and other studies of familial aggregation of lung and other cancers do not include enumeration of, and risk factor data for, all relatives.

Familial aggregation, as shown here and in published studies, is moderate. These findings are consistent with a common susceptibility gene(s) acting to moderately increase risk of cancer [Caporaso and Goldstein, 1995; Houlston and Peto, 1996]. For tobacco-related cancers, breast cancer, and colon cancer, susceptibility associated with polymorphic genes coding for Phase I and Phase II enzymes (i.e., CYP1A1, CYP2D6, GSTM1, NAT2) has been reported. These enzymes play a role in the activation and detoxification of carcinogens. Association studies, however, have often yielded conflicting results [Kawajiri et al., 1990; Sugimura et al., 1995; Tefre et al., 1991; Hirvonen et al., 1992, 1995; Cosma et al., 1993; Shields et al., 1993; Caporaso et al., 1995; Bouchardy et al., 1996; Seigegard et al., 1990; Nazar-Stewart et al., 1993; Nakajima et al, 1995; Cascorbi et al., 1996]. The results from several studies of lung cancer risk suggest that the effects of a metabolic enzyme phenotype or genotype may be more evident at low levels of exposure to carcinogens [Sugimura et al., 1995; Nakachi et al., 1991; Vineis and Martone, 1995], as might occur in the nonsmoking probands. This is further supported by the findings of increased risk among nonsmoking relatives. The identification of these nonsmoking lung cancer cases may serve to characterize families with altered metabolism of carcinogens and increased susceptibility.

In addition to lung cancer, a twofold increased risk in colon cancer has been shown to be associated with the *GSTM1* null genotype [Zhong et al., 1993]. Ambrosone et al. [1995] have reported a fivefold increased risk of postmenopausal breast cancer among heavier smokers with at least one copy of the mutant *CYP1A1* allele. Ambrosone et al. [1996] also reported that *NAT2* genotype modified postmenopausal breast cancer risk associated with smoking. Among slow acetylators, a dose-response relationship between cigarette smoking and breast cancer risk was observed. In a small study, Yang et al. [1996] have shown that lung cancer cases with a homozygous mutant *NAT2* genotype, either alone or in combination with *GSTM1* null genotype were significantly more likely to report a first-degree relative with cancer than lung cancer cases with other genotypes. These findings suggest that shared genotypes at susceptibility loci within families may be partially responsible for familial aggregation of cancers at multiple sites.

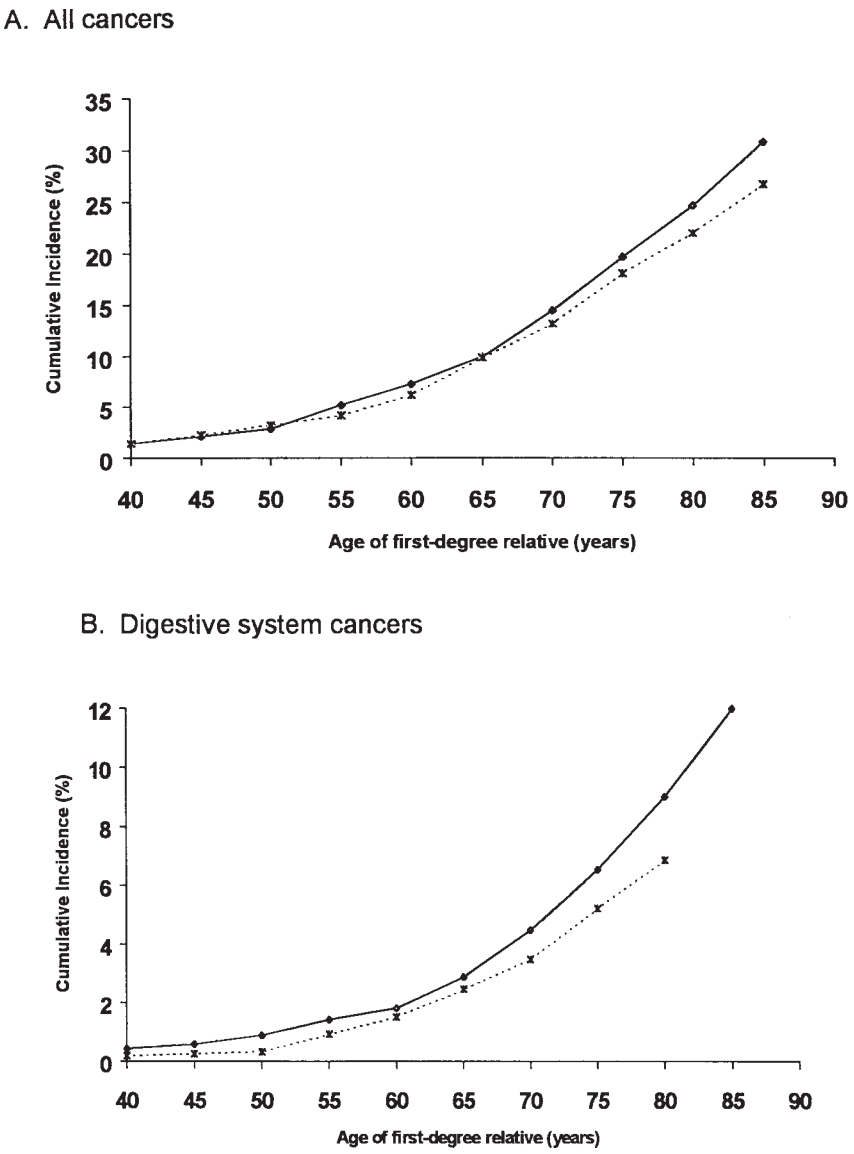
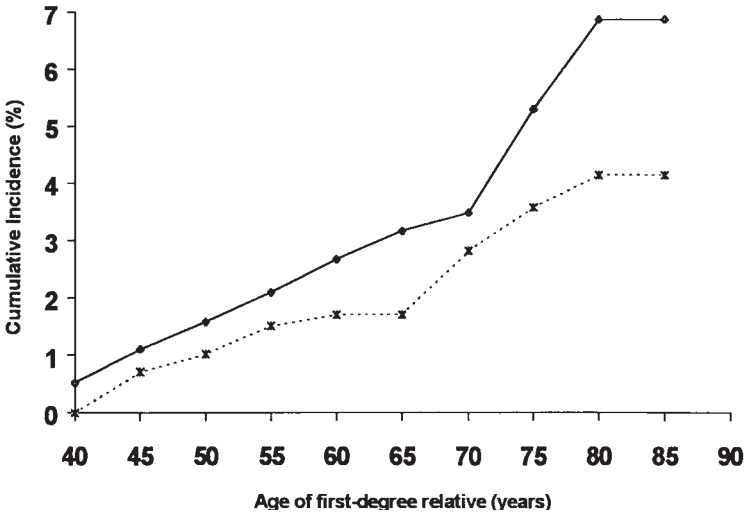


Fig. 1. Cumulative incidence of cancer in first-degree relatives of nonsmoking probands. ♦, case relatives; x, control relatives.

In addition to variations in metabolic enzyme genotypes, microsatellite instability is found in a number of cancers, including colon and lung, and might explain some of the familial aggregation. Most colon cancers in patients with hereditary nonpolyposis colorectal cancer (HNPCC) show microsatellite instability as a result of mutations in one of the mismatch repair genes [Lui et al., 1996]. Families with HNPCC also demonstrate increased risk for cancers of the endometrium, stomach, ovary, small intestines, ureter, and renal pelvis [Giardiello, 1997; Watson and Lynch, 1994]. While

C. Breast cancers



D. Tobacco-associated cancers

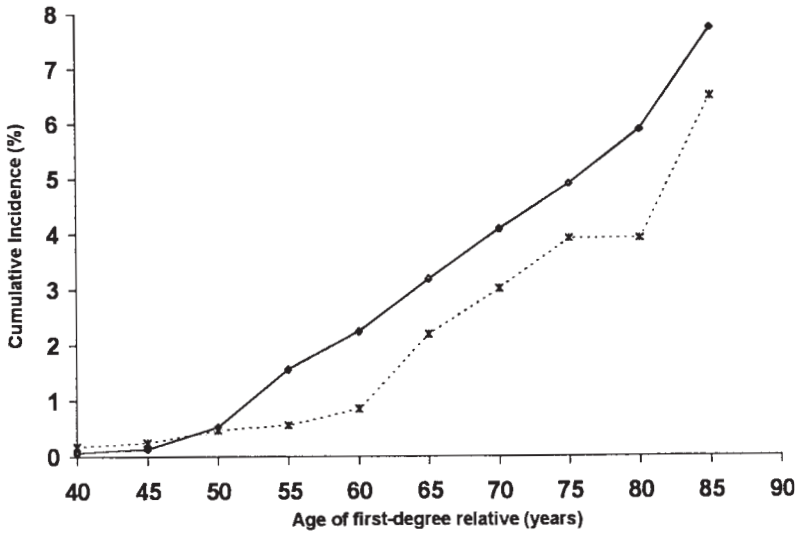


Figure 1. (*continued*).

lung cancer is not found in excess in HNPCC families, lung cancers and sporadic colon cancers have been reported to demonstrate microsatellite instabilities in the range of 7–45% and 13–17%, respectively [Bubb et al., 1996; Shridhar et al., 1994; Merlo et al., 1994; Fong et al., 1995]. Instability at only one locus is common in

TABLE V. Risk Estimates for Cancer Among First-Degree Relatives of Nonsmoking Probands by Age of Diagnosis of the Proband, Metropolitan Detroit, 1984–1987

	Probands age 40–59 years						Probands age 60–84 years					
	Cancer in relatives of cases		Cancer in relatives of controls				Cancer in relatives of cases		Cancer in relatives of controls			
Cancer site	Yes	No	Yes	No	RR[a]	95% CI	Yes	No	Yes	No	RR[a]	95% CI
All cancers	39	309	27	391	1.72	(0.95–3.10)	188	1,313	184	1,437	1.11	(0.87–1.43)
Cancers other than lung	30	318	25	393	1.42	(0.78–2.56)	166	1,335	157	1,464	1.16	(0.89–1.50)
Tobacco-associated sites[b]	11	337	5	413	2.33	(0.83–6.53)	41	1,460	35	1,586	1.29	(0.79–2.12)
Digestive system	13	335	6	412	3.14	(0.76–12.9)	59	1,442	45	1,576	1.42	(0.93–2.17)
Respiratory system	9	339	4	414	2.31	(0.69–7.76)	23	1,478	27	1,594	0.93	(0.51–1.70)
Female breast	4	151	2	205	2.64	(0.41–17.1)	24	728	17	808	1.60	(0.83–3.08)
Female reproductive system[c]	2	153	6	201	0.90	(0.73–3.00)	19	733	17	808	1.52	(0.63–3.70)
Prostate	1	192	1	210	—[d]		11	738	11	785	1.01	(0.43–2.34)

[a]Adjusted for age, race, sex, and smoking status (ever/never).
[b]Includes cancers of the respiratory system, oral cavity and pharynx, esophagus, urinary bladder and kidney.
[c]Includes uterus and ovary.
[d]Too few cancers for analysis.

TABLE VI. Risk Estimates for Cancer Among Smoking and Nonsmoking First-Degree Relatives of Nonsmoking Probands, Metropolitan Detroit, 1984–1987

	Ever smoking relatives						Never smoking relatives					
	Cancer in relatives of cases		Cancer in relatives of controls				Cancer in relatives of cases		Cancer in relatives of controls			
Cancer site	Yes	No	Yes	No	RR[a]	95% CI	Yes	No	Yes	No	RR[a]	95% CI
All cancers	84	539	87	596	1.05	(0.72–1.52)	143	1,083	124	1,239	1.32	(1.003–1.73)
Cancers other than lung	61	562	69	614	0.94	(0.63–1.40)	135	1,091	113	1,250	1.37	(1.03–1.82)
Tobacco-associated sites[b]	35	588	24	659	1.61	(0.91–2.83)	17	1,209	16	1,340	1.16	(0.59–2.27)
Digestive system	22	601	24	659	0.96	(0.52–1.79)	50	1,176	27	1,336	2.01	(1.20–3.37)
Respiratory system	23	600	19	664	1.36	(0.69–2.68)	9	1,217	12	1,351	0.81	(0.35–1.90)
Female breast	6	209	4	239	—[c]		22	670	15	774	1.71	(0.85–3.44)
Female reproductive system[d]	5	210	7	236	0.86	(0.23–3.25)	16	676	16	773	1.11	(0.50–2.44)
Prostate	8	400	4	436	2.23	(0.66–7.52)	4	530	9	558	0.49	(0.15–1.59)

[a]Adjusted for age, race, sex.
[b]Includes cancers of the respiratory system, oral cavity and pharynx, esophagus, urinary bladder and kidney.
[c]Too few cancers for analysis.
[d]Includes uterus and ovary.

these cancers. In a series of sporadic colon cancers with microsatellite instability, only one in 24 contained an exonic mutation in *hMSH2*, suggesting an alternative genetic basis for microsatellite instability in sporadic colon cancer as compared with HNPCC [Bubb et al., 1996]. The frequency of alterations in mismatch repair genes in lung cancer has not been reported and warrants further investigation.

In addition to susceptibility genes, a single gene predisposing to several types of cancer may explain these findings. Only one study has evaluated, by segregation analysis, the pattern of occurrence of lung and other cancers in families. Sellers et al. [1994] found evidence consistent with a major gene influencing age of onset in smoking-associated cancers. Without the collection of family history beyond first-degree relatives, it will be difficult to characterize the spectrum of cancers found in lung cancer families and define a family cancer syndrome if one exists.

An alternative explanation for these findings includes shared environmental risk factors. It is possible that risk factors other than those included in this study, such as diet, cluster in families and account for some of the observed aggregation. The possibility of recall bias and the reliance on proxy interviews must also be considered in explaining these results. In this study, documentation of cancer has been obtained for 49% and 57% of the relatives of cases and controls, respectively. The biggest obstacle in obtaining documentation has been locating medical records for parents and siblings diagnosed decades earlier. Several studies, however, have shown that family members provide accurate reports of first-degree family cancer history [Bondy et al., 1994; Love et al., 1985]. For smoking history, categorization of ever vs. never smoked was used in the final analytic models. This type of information also has been shown to be reported accurately by proxies [McLaughlin et al., 1987].

In conclusion, familial aggregation of cancer, and in particular cancers of the digestive tract, was demonstrated in families identified through nonsmoking lung cancer cases, with highest risk among relatives of cases diagnosed between ages 40 and 59 years. These findings are consistent with the existence of common, low penetrant susceptibility genes. The possibility of a rare, highly penetrant gene predisposing to cancer at multiple sites also exists. A wide range of design strategies, including large population-based studies and family-based studies, using linkage analysis, direct analysis of candidate genes, and studies of phenotypic markers, will be needed to more fully understand the role of susceptibility genes in cancers of multiple sites with moderate familial effects.

ACKNOWLEDGMENTS

This work was supported in part by National Cancer Institute grants R29-CA50383 (A.G.S.) and R01-CA60691 (A.G.S.), a National Institute of Occupational Safety and Health grant R01-OH02067 (G.M.S.), and a National Cancer Institute contract N01-CN05225 (G.M.S.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute. The authors thank Rochelle Steiner for data collection.

REFERENCES

Ambrosone CB, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, et al. 1995. Cytochrome P4501A1 and glutathione S-transferase (M1) genetic polymorphisms and postmenopausal breast cancer risk. Cancer Res 55:3483–3485.

Ambrosone CB, Freudenheim JL, Graham S, Marshall JR, Vena JE, Brasure JR, et al. 1996. Cigarette smoking, N-acetyltransferase 2 genetic polymorphisms, and breast cancer risk. J Am Med Assoc 276:1494–1501.

Anderson KE, Woo C, Olson J, Sellers TA, Zheng W, Kushi LH, et al. 1997. Association of family history of cervical, ovarian, and uterine cancer with histological categories of lung cancer: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prevention 6: 401–405.

Bondy ML, Strom SS, Colopy MW, Brown BW, Strong LC. 1994. Accuracy of family history of cancer obtained through interviews with relatives of patients with childhood sarcoma. J Clin Epidemiol 47:89–96.

Bouchardy C, Benhamou S, Dayer P. 1996. The effects of tobacco on lung cancer risk depends on CYP2D6 activity. Cancer Res 56: 251–253.

Bubb VJ, Curtis LJ, Cunningham C, Dunlop MG, Carothers AD, Morris RG, et al. 1996. Microsatellite instability and the role of hMSH2 in sporadic colorectal cancer. Oncogene 12: 2641–2649.

Caporaso N, Goldstein A. 1995. Cancer genes: single and susceptibility: exposing the difference. Pharmacogenetics 5: 59–63.

Caporaso N, DeBaum MR, Rothman N. 1995. Lung cancer and CYP2D6 (the debrisoquine polymorphism): sources of heterogeneity in the proposed association. Pharmacogenetics 5:S129–134.

Cascorbi I, Brockmuller J, Mrozikiewicz PM, Bauer S, Loddenkemper R, Roots I. 1996. Homozygous rapid arylamine N-actyltransferase (NAT2) genotype as a susceptibility factor for lung cancer. Cancer Res 56:3961–3966.

Cavenee WK, Koufos A, Hansen MF. 1986. Recessive mutant genes predisposing to human cancer. Mutat Res 168:3–14.

Cosma G, Crofts F, Currie D, Wirgin I, Toniolo P, Garte SJ. 1993. Racial differences in restriction fragment length polymorphisms and messenger RNA inducibility of the human CYP1A1 gene. Cancer Epidemiol Biomarkers Prev 2: 53–57.

Fong KM, Zimmerman PV, Smith PJ. 1995. Microsatellite instability and other molecular abnormalities in non-small cell lung cancer. Cancer Res 55:28–30.

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE, Breast Cancer Linkage Consortium. 1994. Risks of cancer in BRCA-1 mutation carriers. Lancet 343:692–695.

Gauderman WJ, Morrison JL, Carpenter CL, Thomas DC. 1997. Analysis of gene-smoking interaction in lung cancer. Genet Epidemiol 14:199–214.

Giardiello FM. 1997. Genetic testing in hereditary colorectal cancer. J Am Med Assoc 278:1278–1281.

Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH. 1994. Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. J Natl Cancer Inst 86:1600–1608.

Hirvonen A, Husgafvel-Pursianinen K, Antilla S, Karjolainen A, Sorsa M, Vainio H. 1992. Metabolic cytochrome P450 genotypes and assessment of individual susceptibility to lung cancer. Pharmacogenetics 2:259–263.

Hirvonen A, Pelin K, Tammilehto L, Karjalainen A, Mattson K, Linnainmaa K. 1995. Inherited GSTM1 and NAT2 defects as concurrent risk modifiers in asbestos-related human malignant mesothelioma. Cancer Res 55: 2981–2983.

Houlston RS, Peto J. 1996. Genetics and the common cancers. In: Eeles RA, Ponder BAJ, Easton DF, Horwich A, editors. Genetic predisposition to cancer.London: Chapman & Hall, p 208–226.

Illis WR, Swanson GM, Satariano ER, Schwartz AG. 1987. Summary measures of occupational history: a comparison of latest occupation and industry with usual occupation and industry. Am J Public Health 77:1532–1534.

Kawajiri K, Natachi K, Luai K, Yoshi A, Shinodo N, Watanabe J. 1990. Identification of genetically high risk individuals to lung cancer by DNA polymorphisms of the cytochrome P4501A1 gene. FEBS Lett 263:131–133.

Li FP, Fraumeni JF Jr. 1969. Soft-tissue sarcomas, breast cancer, and other neoplasms: a familial syndrome? Ann Intern Med 71:747–752.

Love RR, Evans AM, Josten DM. 1985. The accuracy of patient reports of a family history of cancer. J Chronic Dis 38:289–293.

Lui B, Parsons R, Papadopoulos N, Nicolaides NC, Lynch HT, Watson P, et al. 1996. Analysis of mismatch repair genes in hereditary non-polyposis colorectal cancer patients. Nature Med 2:169–174.

Malkin D, Li FP, Strong LC, Fraumeni J Jr., Nelson CE, Kim D, et al. 1990. Germ line p53 mutations in a familial syndrome of breast cancer sarcomas and other neoplasms. Science 250:1233–1238.

McLaughlin JK, Dietz MS, Mehl ES, Blot WJ. 1987. Reliability of surrogate information on cigarette smoking by type of informant. Am J Epidemiol 126:144–146.

Merlo A, Mabry M, Gabrielson E, Vollmer R, Baylin SB, Sidransky D. 1994. Frequent microsatellite instability in primary small cell lung cancer. Cancer Res 54: 2098–2101.

Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian A, et al. 1994. Isolation of BRCA1, the 17q-linked breast and ovarian cancer susceptibility gene. Science 266: 66–71.

Nakachi K, Imai K, Hayashi S, Watanabe J, Kawajiri K. 1991. Genetic susceptibility to squamous cell carcinoma of the lung in relation to cigarette smoking dose. Cancer Res 51:5177–5180.

Nakajima T, Elovaara E, Antilla S, Hirvonen A, Camus AM, Hayes JD, et al. 1995. Expression and polymorphisms of glutathione S-transferase in human lungs: risk factors in smoking-related lung cancer. Carcinogenesis 16:707–711.

Nazar-Stewart V, Motulsky AG, Eaton DL, White E, Hornung SK, Leng Z-T, et al. 1993. The glutathione S-transferase m polymorphism as a marker for susceptibility to lung carcinoma. Cancer Res 53: 2313–2318.

Nelson CL, Sellers TA, Rich SS, Potter JD, McGovern PG, Kushi LH. 1993. Familial clustering of colon, breast, uterine, and ovarian cancers as assessed by family history. Genetic Epidemiol 10:235–244.

Olschwang S, Laurent-Puig P, White GR, Thomas G. 1993. Germ-line mutations in the first 14 exons of the adenomatous polyposis coli gene (APC). Am J Human Genet 52:269–273.

Ooi WL, Elston RC, Chen VW, BaileyWilson JE, Rothschild H. 1986. Increased familial risk for lung cancer. J Natl Cancer Inst 76:217–222.

SAS Institute Inc. 1990. SAS/STAT User's Guide, Version 6, Fourth Edition, Volumes 1–2. Cary, NC: SAS Institute Inc.

SAS Institute Inc. 1997. SAS/STAT Software: changes and enhancements through release 6.12. Cary, NC: SAS Institute Inc.

Schwartz AG, Boehnke M, Moll PP. 1988. Family risk index as a measure of familial heterogeneity of cancer risk: a population-based study in metropolitan Detroit. Am J Epidemiol 128:524–535.

Schwartz AG, Yang P, Swanson GM. 1996. Familial risk of lung cancer among nonsmokers and their relatives. Am J Epidemiol 144:554–562.

Seigegard J, Pero RW, Markowitz MM, Roush G, Miller DG, Beattie EJ. 1990. Isoenzymes of glutathione transferase (class mu) as a marker for the susceptibility to lung cancer: a follow up study. Carcinogenesis 11:33–36.

Sellers TA, Ooi WL, Elston RC, Chen VW, BaileyWilson JE, Rothschild H. 1987. Increased familial risk for nonlung cancer among relatives of lung cancer patients. Am J Epidemiol 126:237–246.

Sellers TA, Elston RC, Stewart C, Rothschild H. 1988. Familial risk of cancer among randomly selected cancer probands. Genetic Epidemiol 5: 381–391.

Sellers TA, Bailey-Wilson JE, Elston RC, Wilson AF, Ooi WL, Rothschild H. 1990. Evidence for Mendelian inheritance in the pathogenesis of lung cancer. J Natl Cancer Inst 82:1272–1279.

Sellers TA, Potter JD, Folsom AR. 1991. Association of incident lung cancer with family history of female reproductive cancers: the Iowa Women's Health Study. Genetic Epidemiol 8:199–208.

Sellers TA, Chen P-L, Potter JD, Bailey-Wilson JE, Rothschild H, Elston RC. 1994. Segregation analysis of smoking-associated malignancies: evidence for Mendelian inheritance. Am J Med Genet 52:308–314.

Shaw GL, Falk RT, Pickle LW, Mason TJ, Buffler PA. 1991. Lung cancer risk associated with cancer in relatives. J Clin Epidemiol 44:429–437.

Shields PG, Caporaso NE, Falk RT, Sugimura H, Trivers GE, Trump BF, et al. 1993. Lung cancer, risk, and a CYP1A1 genetic polymorphism. Cancer Epidemiol Biomarkers Prev 2:481–485.

Shridhar V, Siegfried J, Hunt J, del Mar Alonso M, Smith D. 1994. Genetic instability of microsatellite sequences in many non-small cell lung carcinomas. Cancer Res 54:2084–2087.

Sugimura H, Hamada GS, Suzuki I, Iwase T, Kiyokawa E, Kino I, et al. 1995. CYP1A1 and CYP2E1 polymorphisms and lung cancer, a case-control study in Rio de Janeiro, Brazil. Pharmacogenetics 5:S145–148.

Swanson GM, Schwartz AG, Brown KL. 1985. Population-based occupational cancer incidence surveillance. J Occup Med 27: 439–444.

Tefre T, Ryberg D, Haugen A, Nebert DW, Skaug V, Brogger A, et al. 1991. Human CYP1A1 (cytochrome P_1450) gene: lack of association between the MspI RFLP and incidence of lung cancer in a Norwegian population. Pharmacogenetics 1:20–25.

Vineis P, Martone T. 1995. Genetic-environmental interactions and low-level exposure to carcinogens. Epidemiol 6:455–457.

Watson P, Lynch HT 1994. The tumor spectrum in HNPCC. Anticancer Res 14:1635–1640.

Wooster R, Bignell G, Lancaster J, Swift S, Seal S, Mangion J, et al. 1995. Identification of the breast cancer susceptibility gene BRCA2. Nature 387:789–792.

Wu AH, Fontham ETH, Reynolds P, Greenberg RS, Buffler P, Liff J, et al. 1996. Family history of cancer and risk of lung cancer among lifetime nonsmoking women in the United States. Am J Epidemiol 143:535–542.

Yang P, Romkes M, Schwartz AG, Rittmeyer L, Adedoyin A, Landreneau R, et al. 1996. Polymorphisms at the NAT2* locus associated with increased cancer risk in first-degree relatives of lung cancer patients. Genetic Epidemiol 3:308–309.

Yang P, Schwartz AG, McAllister AE, Swanson GM, Aston CE. 1999. Lung cancer risk in families of nonsmoking probands: heterogeneity by age at diagnosis. Genetic Epidemiol.

Zeger SL, Liang KY. 1986. Longitudinal data analysis for discrete continuous outcomes. Biometrics 42:121–130.

Zhong S, Wyllie AH, Barnes D, Wolf CR, Spurr NK. 1993. Relationship between the GSTM1 genetic polymorphism and susceptibility to bladder, breast and colon cancer. Carcinogenesis 14:1821–1824.