Original Investigation

Familial Risk in Patients With Carcinoma of Unknown Primary

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IMPORTANCE Carcinoma of unknown primary (CUP) accounts for 3% to 5% of all cancers and is associated with poor prognosis. Familial clustering of different cancer sites with CUP is unknown and may provide information regarding etiology, as well as elevated cancer risks in relatives.

OBJECTIVE To quantify the risk of cancer by site in first- and second-degree relatives and first cousins of individuals with CUP.

DESIGN, SETTING, AND PARTICIPANTS Nested case-control study of patients who received a diagnosis of CUP between 1980 and 2010 identified from the Utah Cancer Registry. Population controls with no CUP diagnosis were sex and age matched 10:1 to patients with CUP. Data about relatives were drawn from the Utah Population Database.

MAIN OUTCOMES AND MEASURES Familial aggregation of cancer risk in relatives of cases compared with controls using Cox regression analysis.

RESULTS For the 4160 index patients (median [interquartile range] age, 72 [62-81] years; 47.6% male) who had received a diagnosis of CUP, first-degree relatives were at an elevated risk of CUP themselves (hazard ratio [HR], 1.35 [95% CI, 1.07-1.70]), as well as lung (HR, 1.37 [95% CI, 1.22-1.54]), pancreatic (HR, 1.28 [95% CI, 1.06-1.54]), myeloma (HR, 1.28 [95% CI, 1.01-1.62]), and non-Hodgkin lymphoma (HR, 1.16 [95% CI, >1.00-1.35]) cancers compared with controls without CUP. When the analysis was restricted to relatives of cancer-free controls, additional increased risks for colon (HR, 1.19 [95% CI, 1.06-1.33]) and bladder (HR, 1.18 [95% CI, >1.00-1.38]) cancers were observed. Second-degree relatives of patients with CUP were at a slight increased risk of lung (HR, 1.14 [95% CI, 1.03-1.26]), pancreatic (HR, 1.17 [95% CI, 1.01-1.37]), breast (HR, 1.09 [95% CI, 1.02-1.16]), melanoma (HR, 1.09 [95% CI, >1.00-1.19]), and ovarian (HR, 1.19 [95% CI, 1.02-1.39]) cancers.

CONCLUSIONS AND RELEVANCE Relatives of patients with CUP are at increased risk of CUP and several other malignant neoplasms, including lung, pancreatic, and colon cancer. The present data may suggest sites of origin for CUP and provide cancer risk information for relatives of patients with CUP that can lead to effective intervention. Relatives of patients with CUP should be aware of the elevated risks for lung, pancreatic, and colon cancer and encouraged to modify risk factors and adhere to site-specific population cancer screening.

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Carcinoma of unknown primary (CUP) accounts for 3% to 5% of all human cancer cases and is reported to be the seventh or eighth most frequent category of malignant neoplasm and the fourth most common cancer-related cause of death in both sexes.[1] Cancer of unknown primary is a histologically confirmed cancer for which clinicians are unable to identify a primary tumor after undertaking a standard diagnostic approach. Most cases of CUP are carcinomas: adenocarcinomas, squamous cell carcinomas, and undifferentiated neoplasms. Cancer of unknown primary is recognized as a heterogeneous entity in which the metastatic sites dominate, leading to wide variation in presentation. The combination of advanced stage, aggressive behavior, and uncertain treatment approaches leads to poor prognosis.[1] Median survival of all patients with CUP carcinoma in the United States is 3 months, with a 12-month survival rate of only 15% for adenocarcinomas.[1] Recent improvements in histologic diagnosis have eliminated many cases of small-cell carcinoma, lymphoma, and testicular cancer that had previously been included in this syndrome. However, among cancers that remain categorized as CUP, there has been no improvement in survival for more than 20 years.[2]

Many cancer types exhibit frequent familial excess and evidence of inherited susceptibility. Studies from Utah,[3-6] Iceland,[7] and Sweden[8-11] have suggested excess familial clustering for cancers of the colorectum,[12-15] breast,[16] pancreas,[17] lung,[6,8] prostate,[18] and bladder.[19] For colon and breast cancers, these familial risk observations have even led to prevention guidelines for relatives.[13,14] But for CUP, it is unknown whether relatives are at increased risk of CUP itself, or of other cancers. In addition, the familial clustering of various cancer sites with CUP might suggest primary sites in the index CUP cases and even the need for specific screenings in relatives.

In the present study, we tested the hypothesis that specific cancer risks are increased in relatives of patients with CUP. We constructed a population-based case-control study in Utah, using the genealogical records of the Utah Population Database (UPDB) to estimate the risk of cancers in relatives of index cases who received a diagnosis of CUP compared with relatives of cancer-free controls. Our study design is feasible because of the unique linkage between the statewide cancer registry and comprehensive family pedigrees through Utah genealogy records in the UPDB.

At a Glance

- Carcinoma of unknown primary (CUP) accounts for 3% to 5% of all cancers and is associated with poor prognosis. Familial clustering of different cancers with unknown primary is unknown.
- The purpose of this study was to quantify the risk of cancer by site in relatives of individuals with CUP.
- Of 4160 index patients who received a diagnosis of CUP, first-degree relatives were at an elevated risk of several cancers, most importantly CUP (hazard ratio [HR], 1.35 [95% CI, 1.07-1.70]), lung (HR, 1.37 [95% CI, 1.22-1.54), pancreatic (HR, 1.28 [95% CI, 1.06-1.54]), and colon (HR, 1.19 [95% CI, 1.06-1.33]) cancers.
- Relatives of patients with CUP should be aware of their elevated risks of several cancers, including lung, pancreatic, and colon cancer.
- These individuals should be encouraged to modify risk behaviors associated with lung and pancreatic cancers (ie, smoking cessation) and ensure that they undergo appropriate site-specific population cancer screening tests (ie, colon cancer screening).

Methods

Design

This study was approved by the institutional review boards of the University of Utah and Intermountain Healthcare and by the Resource for Genetic and Epidemiologic Research (http://rge.utah.edu), an administrative oversight board charged in 1982 by executive order of the Governor of Utah to govern access to the UPDB. Written consent was not obtained and was waived due to the retrospective nature of the study.

We performed a retrospective population-based case-control study of CUP diagnosed in the state of Utah between 1980 and 2010 and recorded in the Utah Cancer Registry (UCR). This period was selected because endoscopy and advanced imaging were widely available in the state and it would thus closely reflect present-day practice and minimize misclassification bias of CUP. Deidentified medical information on these patients was merged with pedigree structure in the UPDB genealogies to investigate the descriptive characteristics and familial aggregation.

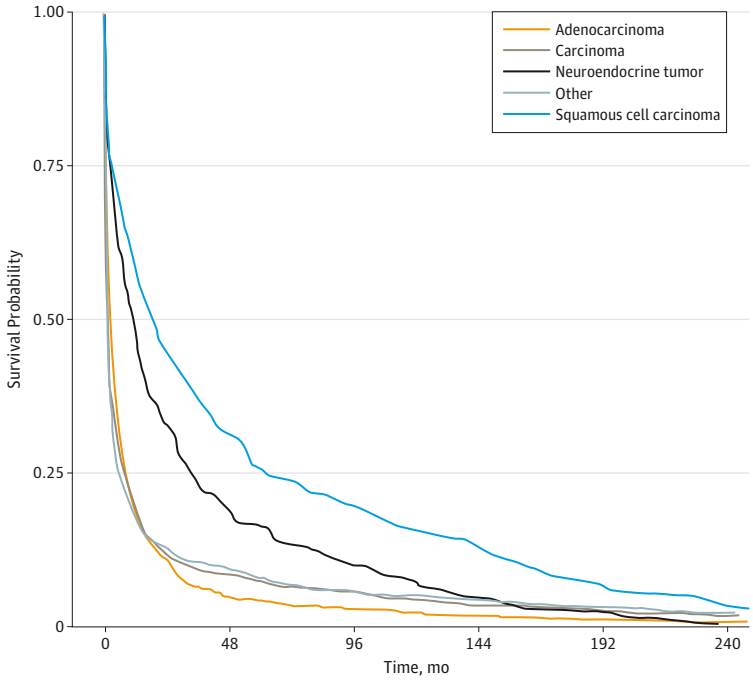
Description of Databases

This investigation takes advantage of unique Utah databases. The UPDB combines genealogies from the Genealogical Society of Utah, dating back to the early 1800s, linked to data from statewide resources, including the UCR and driver's license data, as well as birth and death certificates. There are currently nearly 8 million unique individuals in the database, and the Utah family histories represent pedigrees that may span as many as 12 generations. Previous demographic and genetic analyses have shown that the population recorded in the UPDB is genetically representative of US white and northern European populations with a low level of inbreeding.[20] The UCR is a statewide cancer registry established in 1966, and since 1973 it has been part of the Surveillance, Epidemiology, and End Results network of the National Cancer Institute registries. By state law, all incident cancer diagnoses must be reported to the UCR.

Study Case Population

Electronic records for patients with CUP were derived from the UCR during the period 1980 through 2010. Patients with CUP were defined as those patients for whom the primary site was classified as "unknown primary site" (*International Classification of Diseases for Oncology, Third Edition* [*ICD-O-3*], code 80.9) and active follow-up data were available. To minimize possible confounding from synchronous or metachronous cancer diagnoses, patients with multiple primary cancers were excluded. With respect to analysis of carcinoma by subtype, the following *ICD-O-3* codes were used: adenocarcinoma (8140-8389), squamous cell carcinoma (8050-8089), carcinoma not otherwise specified (8010-8049), and neuroendocrine (8240/3, 8241/3, 8243/3, 8244/3, 8245/3, 8246/3, 8249/3).

Figure. Kaplan-Meier Curve, Comparison of Survival Time in Patients With Carcinoma of Unknown Primary by Tumor Histologic Subtype



No. at risk						
Adenocarcinoma	1511	73	44	27	16	10
Carcinoma	1098	93	61	38	28	20
Neuroendocrine tumor	207	40	21	10	6	1
Other	1018	98	57	44	32	23
Squamous cell carcinoma	326	103	65	43	23	11

Control Group Selection

Population controls with no CUP were selected randomly from the UPDB and matched to cases by sex and birth year in a 10 to 1 ratio. The controls were sampled without replacement and had to have follow-up for at least as long as their respective matched case; follow-up was based on the most recent date when an individual had an event recorded in Utah from vital records (deaths, births, adoptions, marriages, divorces, Utah driver's license registrations and renewals, voter registrations, and statewide inpatient and ambulatory surgical procedures, as described[21]).

A subgroup analysis was performed comparing relatives of CUP cases to relatives of matched controls, restricted to those who were cancer-free to ensure robustness of findings.

Familial Risk Analysis

The recurrence risk in relatives for CUP vs first-primary cancers by known site was calculated in first-degree relatives (FDRs), second-degree relatives (SDRs), and first cousins (FCs) of patients with CUP compared with matched population controls. Using software developed specifically for UPDB kinship analysis, the magnitude of familial risk was estimated by Cox proportional hazard regression models to assess the relative risk of cancer incidence for FDRs, SDRs, and FCs of patients who received a diagnosis of CUP.[3,22,23] This analysis corrects for families being analyzed multiple times because of multiple CUP cases occurring within the family.[24,25] Additional detail regarding familial risk analysis is included in the eAppendix in the Supplement. $P < .05$ was considered statistically significant.

Results

Study Population Characteristics

During the 31-year study period, a total of 4160 patients had a diagnosis of CUP as their sole cancer diagnosis in the UCR, with a median (interquartile range) age of 72 (62-81) years; 47.6% were male. Of these, 1511 (36.3%) had a histologic subtype of adenocarcinoma, 326 (7.8%) were squamous cell carcinoma, 207 (5.0%) were neuroendocrine, and 1098 (26.4%) were carcinoma not otherwise specified. The median (interquartile range [IQR]) overall survival was 2 (1-11) months. Those with adenocarcinoma, carcinoma not otherwise specified, or other malignant neoplasm had median (IQR) overall survival of 3 (1-8), 2 (0-8), and 1 (0-6) month, respectively. Those with histologic subtypes of squamous and neuroendocrine fared better, with survivals of 20 (4-63) and 10 (0-34) months, suggesting some heterogeneity, potentially in stage and/or biological characteristics (**Figure**). **Table 1** shows descriptive features of the index CUP cases and matched controls free of CUP and the subset of controls who were cancer free in this study. Affiliation with the Church of Jesus Christ of Latter-Day Saints (LDS or Mormons), associated with proscriptions against alcohol consumption and cigarette smoking,[26] was comparable for index cases and con-

Table 1. Demographic Characteristics of Patients With Carcinoma of Unknown Primary (CUP)[a]

Characteristic	All CUP	Adenocarcinoma	Carcinoma NOS	Squamous	NET	Other	Controls, Non-CUP	Controls, Cancer-free
Total, No. (%)	4160 (100.0)	1511 (36.3)	1098 (26.4)	326 (7.8)	207 (5.0)	1018 (24.5)	52 036	51 053
Age, median (IQR), y	72 (62-81)	69 (59-77)	73 (63-81)	66 (58-77)	68 (59-76)	77 (66-85)	84 (75-90)	84 (77-90)
Sex, No. (%)								
Male	1982 (47.6)	663 (43.9)	535 (48.7)	208 (63.8)	103 (49.8)	473 (46.5)	25 254 (48.5)	24 676 (48.3)
Female	2178 (52.4)	848 (56.1)	563 (51.3)	118 (36.2)	104 (50.2)	545 (53.5)	26 782 (51.5)	26 377 (51.7)
Survival, median (IQR), mo	2 (1-11)	3 (1-8)	2 (0-8)	19 (4-63)	12 (3-34)	1 (0-6)	NA	NA
Relatives per subject, median (IQR)								
First-degree relative	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	6 (4-9)	6 (3-9)	6 (3-9)	6 (3-9)
Second-degree relative	16 (8-28)	16 (8-28)	17 (9-28)	14 (7-26)	16 (7-26)	18 (8-30)	17 (8-29)	16 (7-28)
First cousin	24 (13-37)	25 (14-39)	24 (12-37)	23 (12-35)	21 (10-36)	23 (13-38)	25 (13-38)	24 (13-38)
Church affiliation, No. (%)								
Active LDS	1037 (24.9)	361 (23.9)	291 (26.5)	59 (18.1)	49 (23.7)	277 (27.2)	14 314 (27.5)	13 778 (27.0)
Inactive LDS	772 (18.6)	285 (18.9)	219 (19.9)	62 (19.0)	31 (15.0)	175 (17.2)	7898 (15.2)	7530 (14.7)
Non-LDS	240 (5.8)	88 (5.8)	71 (6.5)	13 (4.0)	11 (5.3)	57 (5.6)	2446 (4.7)	2618 (5.1)
Unknown	2111 (50.7)	777 (51.4)	517 (47.1)	192 (58.9)	116 (56.0)	509 (50.0)	27 378 (52.6)	27 127 (53.1)

Abbreviations: IQR, interquartile range; LDS, Latter-Day Saints; NA, not applicable; NET, neuroendocrine tumor; NOS, not otherwise specified.

[a] Percentages may not total 100% because of rounding.

Table 2. Familial Cancer Risk in Relatives of Patients With Carcinoma of Unknown Primary (CUP) Compared With 10:1 Controls Matched on Sex and Birth Year

	Hazard Ratio (95% CI)					
	First-Degree Relatives		Second-Degree Relatives		First Cousins	
Cancer Type	CUP-Free Controls	Cancer-Free Controls	CUP-Free Controls	Cancer-Free Controls	CUP-Free Controls	Cancer-Free Controls
CUP	1.35 (1.07-1.70)	1.32 (1.04-1.67)	1.05 (0.89-1.24)	1.06 (0.90-1.25)	1.03 (0.92-1.15)	1.04 (0.93-1.17)
Stomach	1.15 (0.93-1.43)	1.21 (0.98-1.50)	1.13 (0.94-1.34)	1.12 (0.94-1.33)	1.17 (1.04-1.32)	1.16 (1.03-1.31)
Colon	1.12 (1.00-1.26)	1.19 (1.06-1.33)	1.05 (0.96-1.15)	1.09 (0.99-1.19)	1.06 (1.00-1.13)	1.05 (0.99-1.12)
Rectum	1.12 (0.94-1.34)	1.16 (0.97-1.38)	1.00 (0.87-1.15)	1.05 (0.92-1.21)	1.14 (1.04-1.25)	1.18 (1.07-1.29)
Pancreas	1.28 (1.06-1.54)	1.26 (1.05-1.52)	1.11 (0.95-1.29)	1.17 (1.01-1.37)	1.10 (0.99-1.22)	1.09 (0.99-1.21)
Lung	1.37 (1.22-1.54)	1.43 (1.27-1.61)	1.14 (1.03-1.26)	1.07 (0.97-1.18)	1.05 (0.98-1.12)	1.06 (0.99-1.13)
Breast	1.04 (0.95-1.13)	1.08 (0.99-1.18)	1.05 (0.98-1.11)	1.09 (1.02-1.16)	1.02 (0.98-1.07)	1.05 (>1.00-1.10)
Melanoma	1.09 (0.95-1.24)	1.12 (0.98-1.28)	1.06 (0.97-1.15)	1.09 (>1.00-1.19)	1.03 (0.96-1.11)	1.07 (0.99-1.15)
Ovary	1.13 (0.91-1.40)	1.17 (0.94-1.45)	1.20 (1.03-1.41)	1.19 (1.02-1.39)	1.13 (>1.00-1.27)	1.10 (0.98-1.24)
Urinary/bladder	1.10 (0.94-1.29)	1.18 (>1.00-1.38)	1.02 (0.90-1.16)	1.02 (0.89-1.15)	1.05 (0.97-1.14)	1.05 (0.97-1.14)
Non-Hodgkin lymphoma	1.16 (>1.00-1.35)	1.18 (1.02-1.37)	0.88 (0.78-1.00)	0.89 (0.79-1.01)	1.03 (0.95-1.12)	1.04 (0.96-1.13)
Myeloma	1.28 (1.01-1.62)	1.36 (1.07-1.73)	1.01 (0.83-1.23)	1.06 (0.87-1.30)	0.98 (0.85-1.13)	0.94 (0.82-1.09)

trols. For CUP cases and matched controls, the median number of FDRs, SDRs, and FCs with adequate follow-up in Utah was similar, reducing the likelihood of detection bias.

Familial Risk Analysis

Table 2 shows recurrence cancer risks among relatives of index CUP cases compared with controls without CUP based on the degree of relationship. Also shown are familial risk results in relatives of the subset of controls who had no recorded history of any cancer in UCR, and thus were categorized as cancer free. We did not observe statistically significant familial relative risks in FDRs, SDRs, and FCs of cases compared with controls for the following cancers: esophagus, small intestine, appendix, liver, prostate, kidney, thyroid, or leukemia (data not shown).

An elevated risk of CUP, colon, pancreatic, lung, non-Hodgkin lymphoma, and myeloma was observed in relatives of cases compared with relatives of population controls without CUP and in those of the cancer-free control subset. Significant increased familial cancer risks were found among FDRs of patients with CUP for CUP (hazard ratio [HR], 1.35 [95% CI, 1.07-1.70]), pancreatic cancer (HR, 1.28 [95% CI, 1.06-1.54), lung cancer (HR, 1.37 [95% CI, 1.22-1.54]), non-Hodgkin lymphoma (HR, 1.16 [95% CI, >1.00-1.35]), and myeloma (HR, 1.28

[95% CI, 1.01-1.62]), compared with cancer occurrence in FDRs of population controls without CUP. Similar associations were observed for these cancers in FDRs of controls who were cancer free, with additionally elevated risk of colon (HR, 1.19 [95% CI, 1.06-1.33]) and bladder (HR, 1.18 [95% CI, >1.00-1.38]) cancer (Table 2). Second-degree relatives of index cases remained at an increased risk for lung (HR, 1.14 [95% CI, 1.03-1.26]) and ovarian (HR, 1.20 [95% CI, 1.03-1.41]) cancer. When controls were restricted to cancer-free subjects, however, SDRs of patients with CUP were not at increased risk of lung cancer but had a similar risk of ovarian cancer and, additionally, elevated risk for pancreatic cancer (HR, 1.17 [95% CI, 1.01-1.37]), breast cancer (HR, 1.09 [95% CI, 1.02-1.16]), and melanoma (HR, 1.09 [95% CI, >1.00-1.19]). In FCs of CUP cases, a modest increased risk of stomach (HR, 1.17 [95% CI, 1.04-1.32]), rectal (HR, 1.14 [95% CI, 1.04-1.25]), and ovarian (HR, 1.13 [95% CI, >1.00-1.27]) cancers was observed in comparison with relatives of CUP-free controls. These findings were similar in relatives of cancer-free controls for stomach and rectal cancers but not for ovarian cancer. When familial risk in those with active LDS church affiliation was compared with that of those with inactive LDS or non-LDS affiliation, risk estimates did not differ.

Discussion

In this first, to our knowledge, US population-based study of CUP, we observed an increased risk of lung, pancreatic, and colon cancers, non-Hodgkin lymphoma, and myeloma in relatives of patients with CUP. Some of these associations were moderately strong, especially the CUP-lung cancer association, with a 43% elevated risk of lung cancer in FDRs of patients with CUP. Observing these familial associations in a subset of cancer-free controls adds robustness to these findings and provides evidence of an underlying biological or genetic association. These findings are consistent with a familial cancer study conducted in Sweden, where elevated risks for colon, pancreatic, and lung cancers were observed of similar magnitude to our results, along with weaker associations for ovarian, kidney, and bladder cancer.[27]

These findings suggest that the lung, pancreas, and colon may represent primary sites of CUP, in concordance with findings from autopsy studies, which have reported the most common primary sites for CUP as lung (27%), pancreas (24%), liver (8%), kidney or adrenals (8%), and colorectum (7%).[28] We did not observe elevated familial risks for rarer cancers, including tumors of the esophagus, appendix, small intestine, kidney, or liver; nor did we find an elevated risk of leukemia, prostate cancer, or thyroid cancer in relatives of patients with CUP. More importantly, our findings have implications for cancer risks in relatives of patients with CUP as to whether they should be educated on these elevated risks, encouraged to modify risk behaviors, and followed up to ensure that they undergo appropriate population cancer screening tests. Because risks of both lung and pancreatic cancers are moderately increased in relatives of patients with CUP and both are associated with cigarette smoking, our findings may provide physicians with further evidence to encourage smoking avoidance or cessation. The more modest increase in colon cancer risk, at the very least, supports discussion with relatives of the importance of colorectal cancer screening and adhering to general population guidelines to initiate colonoscopy or stool-based testing at age 50 years and complying with recommendations for repeated surveillance.[13,14]

Strengths of this study include use of the unique resources of the UCR to confirm cancer diagnosis linked to genealogical records to determine familial relationships from the UPDB. This avoids ascertainment, referral, and recall bias. This study uniquely examined family risk beyond FDRs and is consistent with an inherited component to cancer risk compared with relatives of those in the population who do not have CUP exclusively, and who are free of any cancer diagnosis. Our results were based on data from a long-term prospective cancer registry with full coverage of the entire state population. Hence, the results are more likely to be generally applicable than those from single centers with a referral center bias, and health care systems outside the United States. The population of Utah is representative of US and European white populations with a low level of inbreeding.[20] Hence, the results are applicable to similar populations in the United States. The findings of our study also represent a time frame when endoscopy and advanced imaging were widely available in the state (1980-2010), minimizing misclassification bias for location of cancers.[29]

Certain limitations of the present study should be noted. Dietary factors, medication use, tobacco exposure, and body mass index were not available for inclusion in our study analysis. It is understood that many environmental factors may be shared by FDRs, which makes distinction between genetic and environmental factors more difficult. Compared to elsewhere, Utah has lower rates of smoking and alcohol use in the population, which could limit generalizability to other populations. However, when familial risk in those with active LDS church affiliation was compared with that of inactive LDS or non-LDS affiliation, risk estimates did not differ. Finally, the conclusions of this study may be weakened by the improved use of immunohistochemical analysis techniques to determine the histotype of metastatic cancers in contemporary practice compared with the study period reported here.

Conclusions

We conducted a population-based case-control study in Utah, showing that relatives of patients with CUP are at increased risk of several malignant neoplasms, including lung, pancreatic, and colon cancer. Even with the benefit of comprehensive clinical assessment, imaging, pathologic analysis, immunohistochemical analysis, and molecular testing, there remains a small proportion of malignant tumors with high mortality in which a primary site of origin cannot be determined. The familial sites shared by CUP have 2 major implications: first, they likely suggest sites of origin for CUP, and second, they provide cancer risk information for relatives of patients with CUP that can lead to effective intervention. Relatives of patients with CUP should be educated on the elevated risks for lung, pancreatic, and co-

lon cancer and encouraged to modify risk behaviors associated with lung and pancreatic cancers (ie, smoking cessation) and ensure that they undergo population cancer screening tests for colorectal cancer. These findings should provide physicians with further evidence to encourage smoking avoidance or cessation and encourage colorectal cancer screening.

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