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Cancer of unknown primary: time trends in incidence, United States

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Abstract
Purpose To describe the epidemiological features and trends of cancer of unknown primary (CUP) in a large and diverse US population.
Methods The Surveillance Epidemiology and End Results registry was used to examine incidence rates, adjusted to the World Segi 1960 population, by demographic and tumor characteristics among patients diagnosed with CUP between 1973 and 2010. Annual percent changes in incidence rates were estimated using Joinpoint regression.
Results The incidence rate of pathologically investigated CUP was 4.1 per 100,000 and is consistent with reports from other countries. In the USA, CUP incidence rates have been decreasing since the early 1980s, 3.6 % per year in the last two decades. The USA experienced decreases earlier than other countries. US males and African Americans had the highest rates of CUP. The rates of non-microscopically confirmed CUP have dropped 2.6 % per year since 1973, but 24 % of CUP patients do not receive microscopic confirmation and 21 % of those with microscopically investigated cancer receive a vague histology (i.e., epithelial) diagnosis. Twenty percent of patients with pathological investigation receive radiation. Patients were twice as likely to be diagnosed with a non-pathologically investigated CUP if they were living in areas with the lowest income quartile relative to areas with the highest income quartile.
Conclusion Although the incidence of CUP is decreasing, we document CUP that may be due to insufficient diagnostic inquiry. Questions raised by the findings in this data provide hypotheses for further epidemiological and biological studies in the elucidation of CUP incidence and treatment.

Keywords Cancer of unknown primary · Incidence · Trends

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Introduction

Cancer of unknown primary (CUP) is a diverse group of metastatic cancers where the primary site cannot be identified. CUP is more likely, than other types of cancer, to have unpredictable clinical behaviors [1]. CUP can metastasize to unexpected locations; for example, occult pancreatic primaries may also metastasize to bone in addition to liver [2]. The inability to identify the primary site of cancer creates clinical challenges because the primary site of cancer usually determines the treatment and overall prognosis [3]. As this is an advanced-stage cancer by definition, patients generally have limited survival time, although this is changing [2]. Knowledge of CUP biology is currently evolving. Hypothesized mechanisms of tumorgenesis suggest the primary tumor may disappear after metastasis, rapidly metastasize before the primary tumor is detectable, rapidly seed metastasize because it is angiogenically

incompetent, or may remain dormant until subclones with angiogenic phenotypes arise then metastasize [4–7].

CUP is an orphan in the cancer epidemiology world [8], especially in the United States. Previous CUP epidemiological studies have focused on Scandinavian, European, and Australian populations [9–14], but the US contribution to population-based epidemiological research is moving slowly. US evaluation of CUP epidemiology is essential due to our racial diversity, the non-comparability of our employment-based insurance system compared to Scandinavian and European healthcare systems, and the availability and use of advanced diagnosis tools in the US medical system. CUP encompasses between three and fifteen percent of all cancer diagnoses and is the fourth most common cause of cancer death, making this a significant area of concern [15–17].

Examination of the descriptive epidemiology of CUP is critical to identify and focus cancer screening and diagnosis as well as informing cancer etiology. We report CUP incidence and trends in the USA over a 37-year period using the National Cancer Institute's Surveillance, Epidemiology, End Results (SEER) Program data.

Methods

Study population

The Surveillance Epidemiology and End Results (SEER) registry provided patient information for this study. SEER has collected data through a network of regional registries since 1973. The number of participating registries expanded in 1992 from 9 registries to 13 registries and expanded again in 2000 to encompass 18 registries. SEER currently covers about 28 % of the US population [18]. Incidence rates were calculated using patients diagnosed with CUP between 2000 and 2010 to obtain the most current estimates. Time trends for gender, histology, and microscopic confirmation were assessed using patients diagnosed between 1973 and 2010. Time trends for race and ethnicity were assessed using patients diagnosed between 1992 and 2010 since data collected before 1992 lack race and ethnicity subgroupings.

Patients diagnosed with CUP were identified through specific published registrar coding rules to maintain standardized case definitions [19–21]. The ICD-O-3 code for CUP is 80.9. We excluded cases diagnosed on a death certificate. Since reporting of CUP is a mixture of extent of diagnostic inquiry and biology, we examined the mutually exclusive groups with microscopic confirmation, called pathological investigation in this report, and patients without pathological investigation. Inclusion of patients diagnosed without pathological investigation is important for public health and disparities research. This group includes patients with positive laboratory tests or marker studies, direct visualization without microscopic confirmation, radiography without microscopic confirmation, a clinical diagnosis, and patients that were missing data. Missing data may represent poor documentation indicative of poor quality of care. Diagnostic workups for CUP may not be complete, given the generally older age at diagnosis and frailty of these patients [22] as survival time for CUP is generally in months [10].

We examined four subgroups of CUP patients with pathological investigation using three variables: microscopic confirmation, histology, and grade. Microscopically confirmed subcategories excluded undifferentiated cancers (the SEER grade variable) and included (1) adenocarcinomas (histological codes 8140–8389), (2) squamous cell carcinomas (histological codes 8050–8089), and (3) epithelial and unspecified (but not undifferentiated; histological codes 8000, 8010–8049). We combined epithelial and unspecified (but not undifferentiated) because both are general categories and may represent inadequate pathological inquiry (perhaps a biopsy needed to be repeated) and may represent inadequate care. We included a mutually exclusive category of (4) microscopically investigated but undifferentiated cancers. Other histological groups were too heterogeneous to draw conclusions and these were omitted from subcategorization. We included a fifth category (5) for CUP diagnosed in the medical record, but not pathologically examined or missing data regarding pathological examination. These patients could have received a positive laboratory test/marker, direct visualization without microscopic confirmation, radiography without microscopic confirmation, or a clinical diagnosis only. Research has demonstrated clinical uncertainty and may contribute to racial and ethnic disparities in the receipt of health care [23].

SEER obtains race and ethnicity data principally from medical records. We focused on three race groups: White, Asian/Pacific Islander, and African Americans. We examined Hispanic and non-Hispanic ethnicity. When ethnicity data were lacking in the medical record, SEER provides ethnicity based on the validated North American Association of Central Cancer Registries Hispanic Identification Algorithm. This algorithm uses name, birthplace, and Hispanic origin to accurately classify ethnicity [24].

The SEER dataset reports receipt of radiotherapy. SEER validation studies report radiotherapy is 90 % complete for some types of cancer [25]. Since lung cancer is a common occult cancer site for CUP, smoking would be an ideal variable to examine, however; individual patient smoking practices were not available in this population-based dataset. Therefore, we examined the proportion of current smokers living within the same small geographical area as the CUP patient. SEER combined data from the Behavioral

Risk Factor Surveillance System (BRFSS) and the National Health Interview Survey (NHIS) to develop estimates for current smoking prevalence in small areas using statistical methods [18]. Three categories of smoking status were assessed as follows: Low proportions included 0–15.6 % of residents reported being current smokers who lived within the same small area as the CUP patient, medium proportions included 15.6–18.6 % of residents reported being current smokers who lived within the small area as the CUP patient, and high proportions included over 18.6 % of residents reported being current smokers who lived within the small area as the CUP patient. These cutoffs represent the lowest quartile, the middle two quartiles, and the highest quartile of current smokers living within the small geographic area. We also examined census-based medium household income. We examined quartiles of this variable.

To obtain estimates for current incidence rates, we used the SEER 18 registry, the most geographically comprehensive dataset, for cases diagnosed between 2000 and 2010. For trends, we used the SEER registry that had data for the longest period, SEER 9 (1973–2010). The SEER 13 (1992–2010) was used for time trends by race, ethnicity since that is when this type of data became available.

Statistical analysis

Incidence rates and 95 % confidence intervals (CIs) were calculated as cases per 100,000 persons, age adjusted and standardized to the World (Segi 1960) standard million population for consistency with international publications on the epidemiology of CUP [3, 26]. Standardizing incidence rates to the 2,000 US standard population calculates incidence rates substantially higher than those standardized to the 1960 World population because of the greater number of older people in the USA [27, 28]. Age-specific and age-adjusted rates were calculated using SEER*Stat version 8.0.4 (NCI, http://www.seer.cancer.gov/seerstat/).

Trend analyses were performed using the SEER Joinpoint regression software version 4.0.1 (NCI, http://surveillance.cancer.gov/joinpoint/). This method assesses changes, or trends, over time by connecting small time segments on a log scale. The annual percent change was estimated for each time segment [29, 30].

Results

Incidence analysis

A total of 79,712 CUP patients were reported in the 18 SEER database for cancers diagnosed between 2000 and 2010. Seventy-six percent of these had a pathological investigation for an incidence rate of 4.1 cases per 100,000 population (Table 1). Incidence rates increase dramatically by age, with average rates for 50–59-year-olds at 8.4 cases per 100,000 population and average rates for patients over 80 years of age at 48.6 cases per 100,000 population. CUP with adenocarcinoma histology was the most common histology with 1.9 cases per 100,000 population followed by squamous cell CUP with 0.6 cases per 100,000 population. Patients with epithelial or unspecified histology (ICD 8000, but not undifferentiated histology) had an incidence rate of 1.1 cases per 100,000 population. Patients diagnosed with CUP without a pathological investigation were 1.0 per 100,000. The rate of missing or no pathology nearly triples between age group 70–79 and aged 80 and over.

The CUP incidence rate for pathologically examined males was 4.7 cases per 100,000 population, and the average incidence among females was 3.6 cases per 100,000 population with a male-to-female incidence ratio of 1.3:1 (Table 1). Males had appreciably higher average incidence rates for squamous and epithelial/unspecified cancers. The average incidence of pathologically examined CUP among Whites was 4.1 cases per 100,000 population, among African Americans was 5.0 cases per 100,000 population, and among Asian and Pacific Islanders (API) was 2.6 cases per 100,000 population. The African American-to-White ratio was 1.2:1 and the API-to-White ratio was 0.6:1. Although the average rates of CUP among Hispanics were slightly lower than non-Hispanics, non-Hispanics had higher rates of CUP with squamous histology.

Almost twenty percent of patients received radiation (Table 2). The proportion of current smokers living in an area where the CUP patient was living did not impact incidence rates; however, patients living in areas with greater smokers were more likely to have a CUP that was not pathologically confirmed. The incidence rate for people living within low-income areas was 4.7 cases per 100,000 population while the average incidence rate for people living within high income areas was 3.9 cases per 100,000 population, a low-to-high incidence ratio of 1:1.2. Patients were twice as likely to be diagnosed with a non-pathologically investigated CUP if they were living in areas with the lowest income quartile relative to areas with the highest income quartile. The average age at diagnosis among Whites was 71.7, for African Americans was 66.1, Asian and Pacific Islanders 68.9 and for Hispanics was 67.5 (data not shown).

Trend analysis

Although for Table 1 we combined CUP that were not diagnostically investigated and missing data because their interpretation is similar, for the trend analyses, we examined both of these categories separately (Fig. 1a). The rate of patients with a SEER diagnosis of CUP based on missing data is small and remained constant through out time. After

Table 1 Average age-specific and age-standardized incidence rates (per 100,000 person-years) cancer of unknown primary by gender and major histological category, race and ethnic group, excluding death certificate

	Age specific					Age-adjusted incidence	*N*
	<50	50–59	60–69	70–79	80+		
Overall							
Pathological investigation (microscopically confirmed)[a]	0.6	8.4	18.8	34.7	48.6	4.1	57,937
Adenocarcinoma	0.2	3.8	9.1	17.7	23.9	1.9	27,858
Squamous	0.1	1.7	2.8	3.7	5.3	0.6	8,037
Epithelial/unspecified	0.1	2.1	5.1	10.0	14.9	1.1	16,047
Undifferentiated	0.0	0.2	0.4	0.8	1.1	0.1	1,262
No/missing pathology	0.1	1.1	3.4	9.2	33.6	1.0	18,183
Men							
Pathological investigation	0.7	9.8	21.8	39.7	56.5	4.7	29,091
Adenocarcinoma	0.2	3.9	9.7	18.6	23.7	2.0	12,449
Squamous	0.2	2.6	4.3	5.4	8.8	0.9	5,499
Epithelial/unspecified	0.2	2.6	6.2	13.0	19.9	1.4	8,786
Undifferentiated	0.0	0.2	0.4	1.0	1.2	0.1	672
No/missing pathology	0.1	1.4	3.9	10.4	34.5	1.1	7,859
Women							
Pathological Investigation	0.6	7.3	16.5	31.4	43.5	3.6	28,846
Adenocarcinoma	0.3	3.6	8.5	17.0	23.9	1.9	15,359
Squamous	0.1	0.8	1.5	2.4	3.4	0.3	2,538
Epithelial/unspecified	0.1	1.9	4.6	8.7	13.4	1.0	8247
Undifferentiated	0.0	0.2	0.7	0.7	0.8	0.1	590
No/missing pathology	0.1	0.9	2.9	8.3	33.1	0.9	10,324
White							
Pathological investigation	0.6	8.3	18.9	35.3	49.8	4.1	47,973
Adenocarcinoma	0.2	3.6	9.0	17.8	24.1	1.9	22,814
Squamous	0.1	1.8	3.0	4.0	5.7	0.6	6,960
Epithelial/Unspecified	0.1	2.0	5.4	10.8	16.1	1.2	14,123
Undifferentiated	0.0	0.2	0.4	0.5	1.0	0.1	1,062
No/missing pathology	0.1	1.1	3.3	9.3	33.8	1.0	15,246
African American							
Pathological investigation	0.8	11.9	23.7	38.1	46.8	5.0	6,296
Adenocarcinoma	0.4	5.9	12.4	20.9	26.8	2.6	3,270
Squamous	0.1	1.7	3.1	3.3	3.0	0.6	703
Epithelial/unspecified	0.3	3.1	6.4	10.5	13.9	1.4	1,748
Undifferentiated	0.0	0.2	0.4	0.7	1.0	0.1	128
No/missing pathology	0.1	2.0	5.0	11.8	36.7	1.4	1,915
API/NA[b]							
Pathological investigation	0.4	5.0	11.2	22.6	32.2	2.6	3,260
Adenocarcinoma	0.2	2.4	5.5	12.0	16.3	1.3	1,624
Squamous	0.1	0.6	1.1	1.4	2.5	0.2	298
Epithelial/unspecified	0.1	1.6	3.6	7.4	10.5	0.8	1,028
Undifferentiated	0.0	0.1	0.2	0.7	0.3	0.1	68
No/missing pathology	0.0	0.6	1.9	5.8	25.8	0.6	970
Hispanic[c]							
Pathological investigation	0.5	7.0	17.3	34.0	49.9	3.8	5,456
Adenocarcinoma	0.2	3.3	9.4	17.6	24.8	1.9	2,736

Table 1 continued

	Age specific					Age-adjusted incidence	*N*
	<50	50–59	60–69	70–79	80+		
Squamous	0.1	0.9	1.4	2.7	3.8	0.3	503
Epithelial/unspecified	0.1	2.1	5.0	10.8	17.6	1.2	1,687
Undifferentiated	0.0	0.2	0.5	1.1	1.0	0.1	161
No/missing pathology	0.1	1.0	3.0	9.8	38.7	1.0	1,601
Non-Hispanic[b]							
Pathological investigation	0.6	8.6	18.9	34.7	48.5	4.1	52,481
Adenocarcinoma	0.2	3.8	9.0	17.7	23.8	1.9	25,122
Squamous	0.1	1.8	3.0	3.8	5.4	0.6	7,534
Epithelial/unspecified	0.2	2.3	5.4	10.6	15.6	1.2	15,346
Undifferentiated	0.0	0.2	0.4	0.8	1.0	0.1	1,101
No/missing pathology	0.1	1.1	3.4	9.2	33.2	1.0	16,582

SEER 18, November Submission, 2000–2010

[a] Not all histologies are subcategorized, only the largest categories

[b] API/NA: Asian, Pacific Islander and Native American

[c] Hispanic ethnicity is not mutually exclusive from the race groups (White, African American and API/NA)

Table 2 Patient and tumor characteristics of cancer of unknown primary by gender and major histological category, race and ethnic group, SEER 18, November Submission, 2000–2010

Characteristics	Pathological investigation			No pathology		
	Rate per 100,000	*N*	%	Rate per 100,000	*N*	%
Microscopic confirmation						
Age <50	0.6	5,233	9.0	0.1	467	3
50–59	8.4	9,401	16.2	1	1,078	7
60–69	18.8	12,946	22.3	2.9	2,010	13
70–79	34.7	16,236	28.0	8.1	3,934	25
Over age 80	48.6	14,121	24.4	29.3	8,333	52
Radiation						
Administered	0.9	11,192	19	0.0	705	5
Not administered	3.1	45,005	78	0.8	14,298	90
Refused	0.0	562	1	0.0	496	3
Unknown	0.1	1,178	2	0.0	323	2
Smoking proportion[a]						
Low	4.7	3685	17	0.9	905	14
Medium	4.7	7,267	35	1.0	2,018	30
High	4.7	11,531	51	1.2	3,684	56
Median household income						
Low	4.7	3,815	6	1.6	1,500	8
Medium low	4.5	3,828	7	1.3	1,378	8
Medium high	4.2	22,475	39	1.1	7,345	40
High	3.9	27,802	48	0.8	7,959	44

[a] Includes 2000–2003 only

a period of increasing adenocarcinoma CUP rates between 1973 and 1980, adenocarcinoma non-significantly fluctuated until 1989 and has been declining ever since; the APC was −2.8 (−3.5, −2.0) with faster declines beginning in 1998, APC = −5.3 (−5.8, −4.7) (Fig. 1b). Statistically significant declines in epithelial and not otherwise specified CUP were observed during the entire period of observation, from 1973 to 2002, APC = −3.3 (−4.8, −1.9), but faster declines were observed after 2003, APC = −5.4 (−7.8, −3.0). CUP with diagnosed without pathology has declined, APR = −1.6 (−2.1, −1.1), faster in recent years, APR = −2.8 (−3.4, −2.3). CUP with squamous cell histology began declining in 1987, APC = −1.6 (−2.1, −1.2). Undifferentiated CUP has been declining since 1979, APC = −6.1 (−7.1. −5.0), but has experienced a steep declines since 1995, APC = −17.6 (−20.1, −14.8).

Figure 2 displays CUP incidence trends by race and ethnicity. Both pathologically examined and non-pathologically examined African American CUP rates declined the fastest (Fig. 2a, b). Although the trends appear similar in

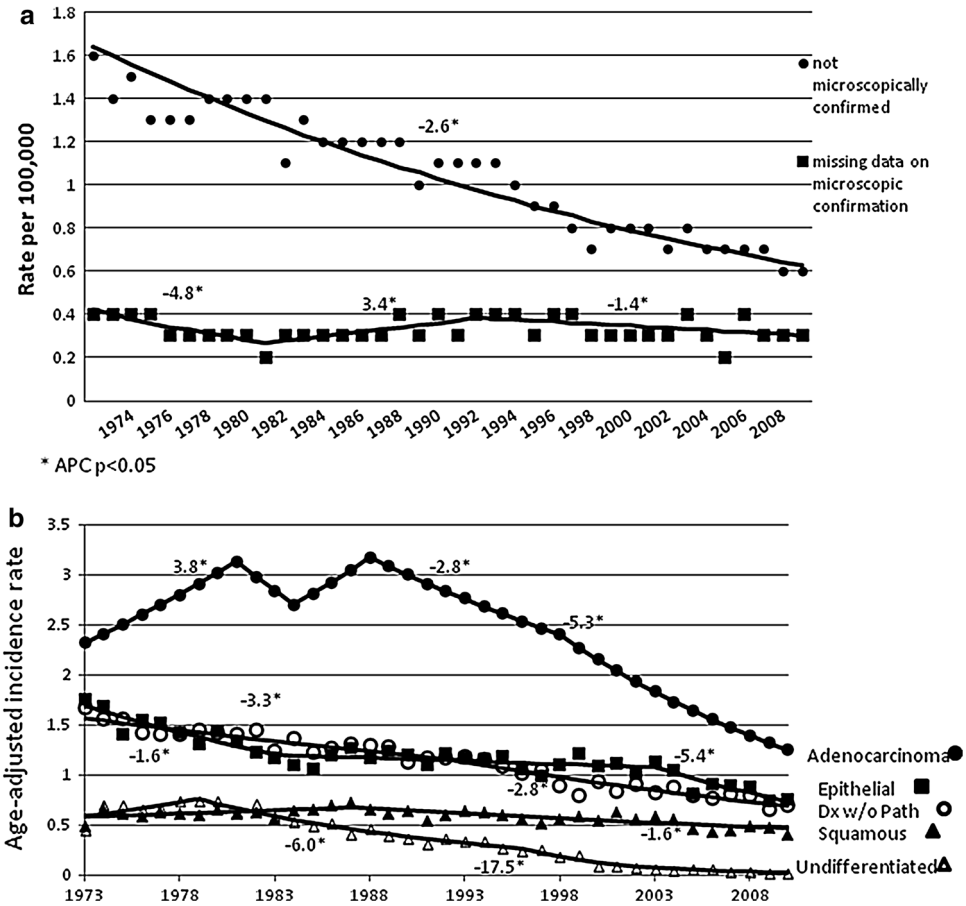

Fig. 1 **a** Incidence rate and annual percent change (APC) of non-microscopically confirmed cup and missing data by year, SEER 1973–2010, November 2012 submission; **b** Trends of CUP incidence rates, annual percent change (APC) for histology groups, SEER 1973–2010, November 2012 submission

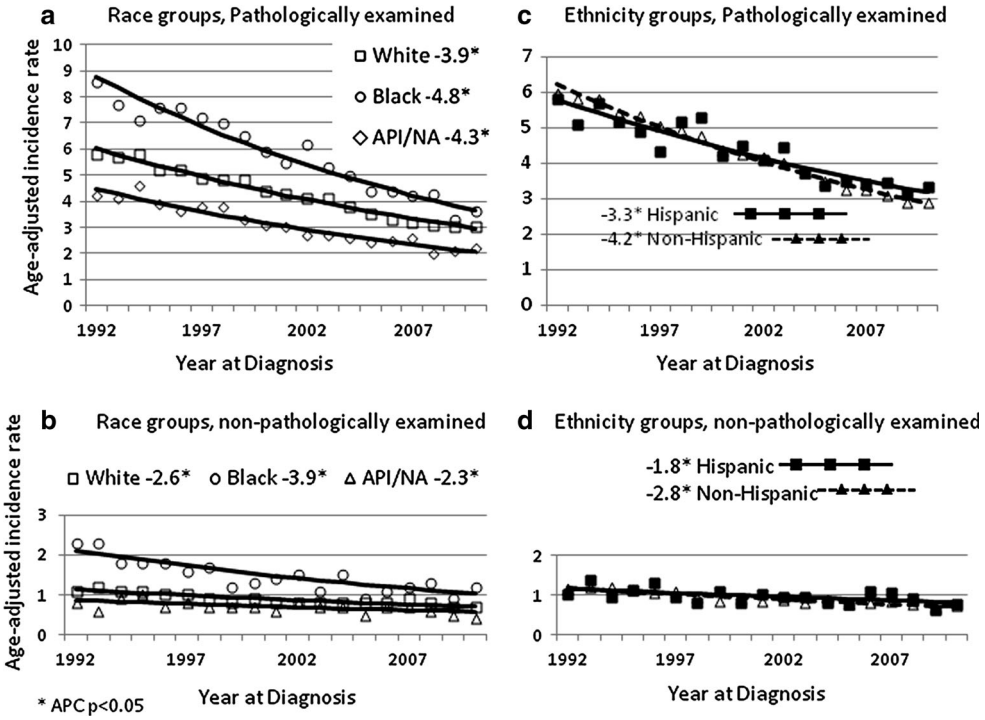

Fig. 2 Trends of CUP incidence rates, annual percent change (APC) for race and ethnic groups, SEER 1992–2010, November 2012 submission. **a** Race groups, pathologically examined; **b** Race groups, non-pathologically examined; **c** Ethnicity groups, pathologically examined; **d** Ethnicity groups, non-pathologically examined

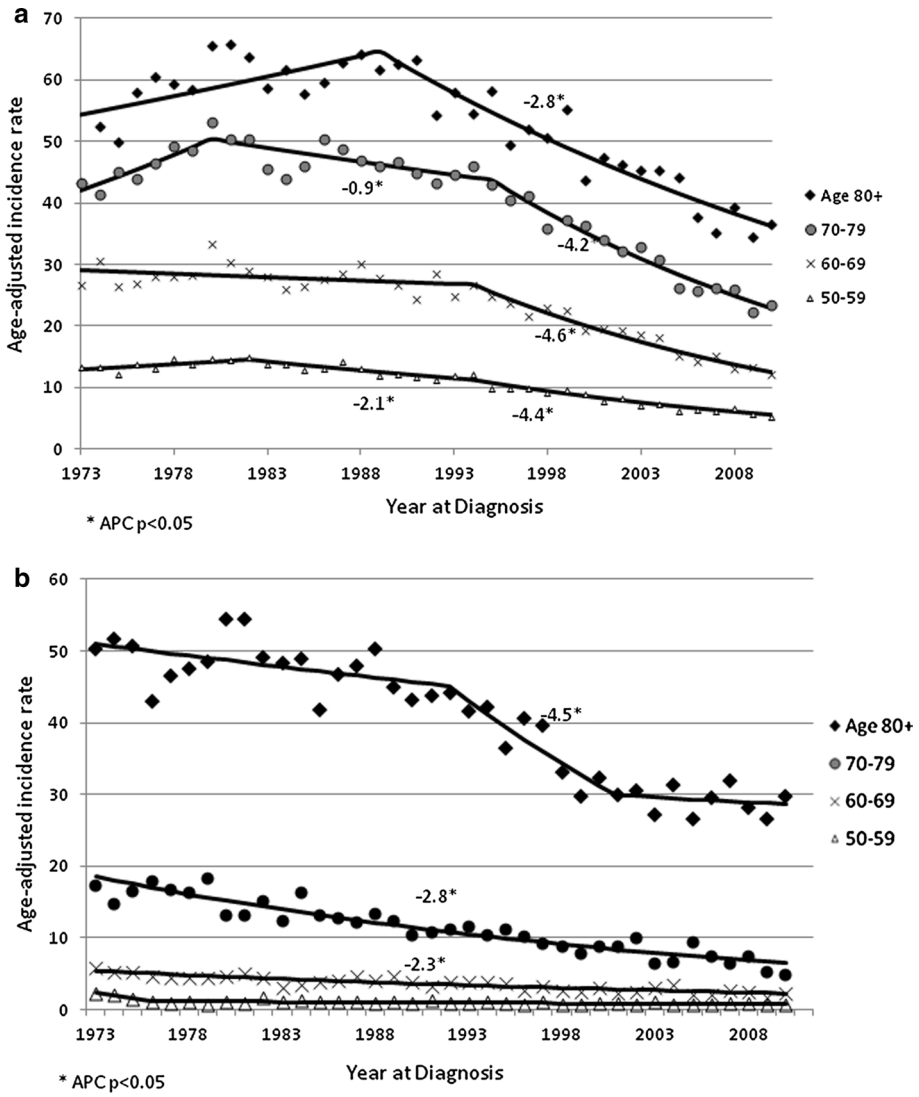

Fig. 3 **a** Trends of pathologically examined CUP incidence rates, annual percent change (APC) for age groups, SEER 1973–2010, November 2012 submission; **b** Trends of non-pathologically examined CUP incidence rates, annual percent change (APC) for age groups, SEER 1973–2010, November 2012 submission

Fig. 2c, d, non-Hispanic rates declined faster than Hispanic rates of CUP, $p = 0.005$.

Figure 3a, b displays the trends by age group. For pathologically investigated CUP, declines among the oldest CUP patients began in 1986 while declines among the 70–79 age group began earlier (Fig. 3a). The oldest age group has the highest rates of non-pathologically confirmed CUP but since 2000, declines have stalled. See Fig. 3b.

Figure 4a, b shows trends by gender. Statistically significant decreases among males began in 1992, APC = −4.2 (−4.7, −3.8). Statistically significant decreases among females began in 1988, APC = −2.3 (−2.9, −1.4) with faster declines beginning in 1999, APC = −4.9 (−5.6, −4.2). Non-pathologically investigated CUP has decreased steadily over time (Fig. 4b).

Discussion

This is the first report, to our knowledge, to examine population-based pathologically examined and non-examined CUP incidence rates and trends among race and ethnic groups in the United States over a 34-year period using SEER registry data. CUP incidence is often overlooked due to its heterogeneous biology and a lack of physician consensus on appropriate diagnosis tools and treatments [6, 9]. By using the SEER registry data, we were able to begin tracking the burden of CUP in the US population. Population-based cancer trends have been reported in European, Scandinavian, and Australian countries while institution-based studies have been conducted in the USA. This study represents an expansion of CUP epidemiology and is an

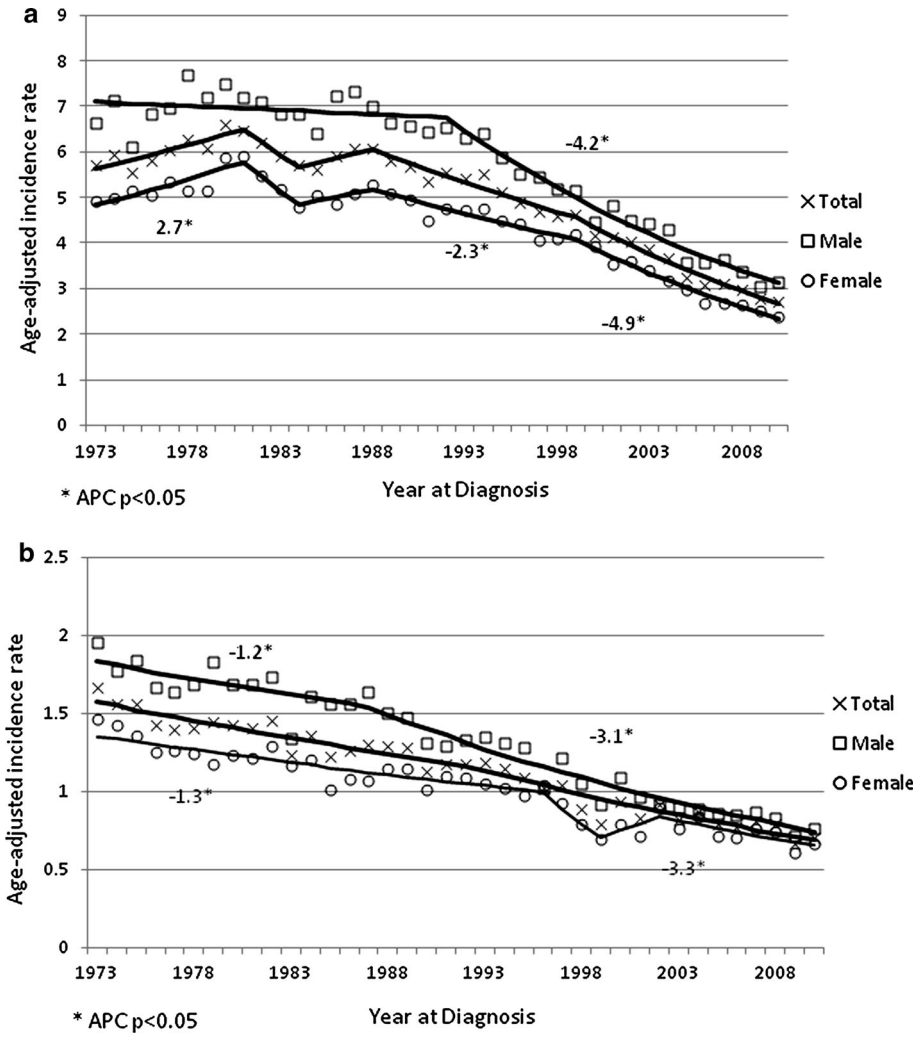

Fig. 4 **a** Trends of pathologically examined CUP incidence rates, annual percent change (APC) by gender, SEER 1973–2010 November 2012 Submission; **b** Trends of non-pathologically examined CUP incidence rates, annual percent change (APC) by gender, SEER 1973–2010, November 2012 submission

important step toward developing a broader research base including population-based diagnostic patterns that can inform CUP guidelines as well as inform etiological and clinical research.

Adenocarcinomas comprised about 48 % of all CUPs with diagnostic investigation, which is consistent with other population-based studies [3]. In Scandinavian countries, squamous histology makes up 4 % of all CUPs, but in our study, squamous cell carcinomas made up 14 % of all CUP. This proportion can double depending on the patients examined: squamous histology makes up about 9 % of all CUP in women, Asian/Pacific Islanders and Hispanics to 18 % in males. Cases diagnosed without pathological investigation made up 24 % of cases in SEER relative to 21 % in Scandinavian populations. This may be due to our insurance structure and uninsured in our population.

US males were more likely to be diagnosed with CUP relative to females. This is observed in some but not in all other countries. In Australia, males were 30 percent more likely to be diagnosed with CUP [31]. Institution-based studies in Tunisia and the Netherlands reported CUP were more common in males [11, 32], but Shu et al. [3] found that females in Scandinavian registry data had slightly higher CUP rates than males. Shu et al. reported the rate for female adenocarcinoma CUP was 3.2 per 100,000 and for males was 2.5 per 100,000. The authors attributed higher female CUP rates to higher female lung cancers among the Scandinavian population. Researchers have reported the most common sites for occult cancers diagnosed as CUP are lung, pancreas, kidney, liver, colon or rectum, genital system, and stomach cancers [33].

Higher rates of common occult sites may also explain the higher CUP rates among males compared to females in the USA. In the USA, males are 30 % more likely than females to be diagnosed with all cancers combined, but males are 47 % more likely to be diagnosed with lung cancer, 200 % more likely to be diagnosed with liver cancer, 90 % more likely to be diagnosed with kidney cancer, and 30 to 33 % more likely to be diagnosed with pancreatic cancer and colorectal cancer [34]. It is plausible that the higher CUP

rates in males in theUSA are due to higher rates of cancer, especially some common types of occult cancers.

The higher CUP incidence rates among African Americans might be related to incidence rates in these specific occult sites. For example, relative to Whites, African American men are 20 % more likely to be diagnosed with lung and colon cancer than Whites, 40 % more likely to be diagnosed with pancreatic cancer, 60 % more likely to be diagnosed with liver cancer but less likely to be diagnosed with stomach cancer [34]. Furthermore, African Americans are more likely to be diagnosed with late stage lung, colorectal cancer, and pancreatic cancer [33, 35], and CUP by definition has metastasized.

On the other hand, African Americans also had the higher rates of epithelial and CUP without pathological investigation compared to other race groups. The histology code for epithelial is a general code and upon further diagnostic testing, many of these epithelial cancers might be coded to another histology. Thus, higher CUP incidence among African Americans may also reflect less access to or use of diagnostic services [17].

Our finding that Hispanics had lower rates of CUP than non-Hispanics is supported by decade's worth of studies examining better health outcomes in Hispanics despite low socioeconomic status. Hispanic smoke less [36] and have better health behaviors [37], which may reduce their cancer burden, especially when younger. On the other hand, Hispanics also have less insurance coverage [38] for diagnostic tests to identify an occult primary site which may result in a CUP diagnosis. This may explain the higher rate of CUP with missing or no pathology among Hispanics.

CUP incidence rates declined earlier in the USA compared to other countries. CUP incidence trends United States peaked at 6.6 per 100,000 in 1980 while Scandinavian peaked at 8 per 100,000 in the late 1990s [3]. Although Australia did not standardize to the World Sigi 1960 standard, thier incidence peaked between 1993 and 1996 [31]. Reported reasons for the observed CUP incidence decrease in Scandinavian countries included decreasing autopsy rates, decreased incidence of common sites of hidden primaries, and the increased use of modern diagnostic methods.

The US decline in the 1980s appears to be driven by females. Although the incidence of some common occult sites, such as lung and gastrointestinal cancers, has decreased during the study period, others have increased as follows: pancreas, kidney, and liver [30]. The USA is well known for our liberal use of imaging techniques since they became available in the early 1980s [39, 40]. Furthermore, breast cancer incidence and CUP incidence in women were relatively stable between 1973 and 1980. Several large clinical trials regarding screening mammography with both positive and negative results were conducted in the late 1970s and 1980s, which increased awareness regarding mammography [41] and thus breast cancer incidence increased throughout the 1980s until the late 1990s [42]. At the same time, CUP incidence in women began to decrease. The improved method to detect breast cancer may have decreased the risk of a small occult breast tumor remaining undetected,therefore, reduced a CUP diagnosis in women during the same time period.

Although CUP rates remain higher among African Americans, their rate decline was faster than Whites over the time period examined. This pattern may reflect the attention to racial inequalities over the past couple of decades regarding access to health care among African Americans [17].

As with all population-based research, there are limitations with this report. First, CUP is a changing diagnosis, and as soon as the primary cancer is identified, the diagnosis will be changed from CUP to the formerly occult primary site. CUP is most certainly underestimated. Reimbursement in the USA for cancer treatment is much more favorable among patients who are diagnosed with a specific type of cancer rather than CUP. Therefore, many CUP patients are classified as having a specific cancer type based on the physician's best guess so that their reimbursed treatment options are maximized. In fact, one of the objectives of this study is to improve awareness of CUP and provide preliminary data for patient selection for biological and clinical studies. This would minimize the need for best guess as to the primary site to provide reimbursement for physicians treating CUP patients. Improved diagnostics (immunohistochemistry and more recently, molecular gene expression profiling) have improved the ability to detect the tissue of origin, even if an anatomic primary site is not found. These patients are increasingly reported and recorded as having cancer from the predicted site rather than CUP. This could be an area of further research. Since all CUP patients are diagnosed with advanced stage, researchers have described CUP tumors by the extent of lymph node involvement [2, 3]. This information was missing in our dataset for patients diagnosed before 2004. In 2010, there were almost no patients receiving microscopic confirmation through immunophenotyping or genetic studies. This is most certainly an artifact of cancer reporting. When newer data become available in SEER, this variable can be examined. We did not use mutually exclusive race and ethnic groups due to concerns about the population estimates (denominator data for the incidence rates). The SEER dataset lacks complete diagnostic workup information, which may shed light on the proportion of CUP patients that have unknown histology. We cannot tell whether this is due to biological factors or a lack of diagnostic tests. Urban et al. [17] suggested that the registry develop a minimum diagnostic workup CUP category and a category where minimum diagnostic workup was not done. Other important variables in having a minimum diagnostic workup would be if

further tests were refused by the patient or perhaps not covered by insurance.

In spite of these limitations, this study provides information on cancer trends among CUP patients that will serve as critical evidence to inform future research. This could include research ranging from social and behavioral research to reasons patients may refuse treatment or may not be able to access diagnosis modalities. This research can help inform etiological research to help identify specific subgroups of CUP patients to policy research to ensure vulnerable and disadvantaged patients have access to advanced diagnostic modalities.

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