J Gastrointest Surg (2015) 19:743–750
DOI 10.1007/s11605-014-2726-7

ORIGINAL ARTICLE

The Rise in Appendiceal Cancer Incidence: 2000–2009

Schelomo Marmor · Pamela R. Portschy · Todd M. Tuttle · Beth A. Virnig

Received: 8 October 2014 / Accepted: 8 December 2014 / Published online: 6 January 2015

Abstract
Purpose *Appendiceal cancer* is a rare and potentially aggressive malignancy. The objectives of this study were to characterize secular demographic patterns of disease and to determine survival by using a population-based data source.
Methods Using the Surveillance, Epidemiology, and End Results database, we conducted a retrospective cohort analysis of patients treated from 2000–2009.
Results We identified 4765 patients with appendiceal cancer. The incidence of appendiceal cancer increased by 54 % from 2000 (0.63 per 100,000) to 2009 (0.97 per 100,000 population). Incidence rates increased across all tumor types, stages, age groups, and gender. The most common malignancies were mucinous adenocarcinoma (38 %), followed by carcinoids (28 %), adenocarcinoma-not otherwise specified (NOS) (27 %), and signet ring cell adenocarcinoma (7 %). Larger tumor size and older patient age were significantly associated with higher relative odds of distant disease at diagnosis ($P<0.0001$). Patient and demographic characteristics were significantly associated with higher relative hazard of death ($P<0.0001$).
Conclusions Although appendiceal cancer is rare, the incidence increased significantly in the USA from 2000 to 2009. The cause of this trend is not obvious. We did not observe increases differentially associated with stage, histology, or demographic characteristics. Further investigation is needed to examine factors underlying this increase.

Keywords *Appendiceal Cancer* · SEER program · Survival

Introduction

Appendiceal cancer is a rare and frequently aggressive malignancy that includes a variety of histological subtypes. Current estimates suggest that the incidence of appendix tumors is approximately 0.12 cases per 100,000 people per year.[1] While rare, appendiceal cancers are associated with considerable mortality. This poor survival is due in part to the frequency of late stage at diagnosis.

S. Marmor (✉) · P. R. Portschy · T. M. Tuttle
Department of Surgery, School of Medicine, University of Minnesota, 420 Delaware Street S.E., Minneapolis, MN 55455, USA
e-mail: marm0014@umn.edu

B. A. Virnig
Division of Health Policy & Management, School of Public Health, University of Minnesota, Minneapolis, MN, USA

Likely due to its relatively low incidence and variety of histological subtypes, appendiceal cancer has not been a focus of epidemiological investigation and is not explicitly included in publications such as the American Cancer Society's "Cancer Facts and Figures". Without information regarding risk factors, studies have generally focused on monitoring incidence over time.[2–4] Since the late 1990s, three important changes in medical practice have potentially influenced the assessment of the incidence of appendiceal cancer. In 1999, the World Health Organization (WHO) emphasized the importance of differentiating between ovarian and appendiceal cancers as they can easily be confused. At about this same point, screening for colon cancer using colonoscopy became increasingly emphasized and widespread. Colonoscopy may identify the appendiceal orifice and allow for increased recognition of tumors of appendix origin. Finally, the use of CT scanning has markedly increased since the late 1990s. In an analysis using the National Hospital Ambulatory Medical Care Survey, the use of CT scans increased by 330 % in emergency departments from 1996 to 2007.[5] This practice may lead to the diagnosis of more tumors of the appendix.

The objectives of this study were to explore demographic and temporal trends in the incidence of appendiceal cancer and identify factors associated with late stage at diagnosis and differences in survival.

Methods

The Surveillance Epidemiology and End Results (SEER) program is a population-based cancer registry that was founded in 1973 by the National Cancer Institute (Bethesda, MD) and, as of 2000, includes 17 regional registries representing approximately 28 % of the US population.[6] The SEER cancer registries provide population-based information on cancer incidence, treatment, and survival. In addition to treatment and survival information, SEER currently collects detailed information on patient demographic and tumor characteristics including age, race, tumor grade, stage, nodal testing, and histology.[6]

We identified all appendiceal cancer patients in the SEER registries between 2000 and 2009. We selected patients from the SEER database for inclusion in our study using the International Classification Disease for Oncology, 3rd edition (ICD-O3) topography code of appendix neoplasms (18.1).

We divided these tumors into two basic histologic categories: carcinoid (SEER histology codes: 8013, 8240–8246, 8249, 8574) and adenocarcinoma; we further divided adenocarcinoma into three categories adenocarcinoma-not otherwise specified (NOS) (8000, 8010, 8140, 8144, 8210, 8211, 8220, 8255, 8260–63, 8440), mucinous adenocarcinoma (8470, 8471, 8480, 8481), and signet-ring cell adenocarcinoma (8490). We excluded SEER histology codes that may have included either in situ or adenomatous tumors. Tumor size was categorized into four groups: <1, 1 to 1.9, 2.0 to 4.9, or 5 cm+ and missing. Cancer stage was defined using SEER historic stage as localized, regional, distant, and unstaged. Age at diagnosis was grouped into categories 18–39, 40–49, 50–59, 60–69, 70–79, and 80 years or greater. Race was grouped into three categories: white non-Hispanic, black, and all others. Step-wise ascertainment of our study cohort is listed in Appendix 1.

We excluded cases that were diagnosed before age 18 or after 80 years of age, those diagnosed by death certificate or autopsy, appendiceal cancers that were reported by a nursing home, and those without microscopic confirmation of cancer.

Statistical Analysis

We calculated incidence rates per 100,000 population for appendiceal cancer overall, by histology, gender, age, and for each year of our study period (2000 through 2009). Differences in rates were tested using two-sided chi-square tests to assess statistical significance. We constructed a logistic regression model to assess changes in rates over time adjusting for age, gender, and race. We assessed the relative odds of distant disease at diagnosis (vs. localized or regional stage) in each year (2000–2009) compared to 2000. All regression models included the patients' age, race, gender, histology, tumor size, diagnosis year, and registry.

Kaplan-Meier methods were used to assess unadjusted conditional survival by histology grouping. Multivariable Cox models were used to compare the impact of histology on factors associated with 5-year relative hazard of death among appendiceal cancer patients while adjusting for covariates.

All statistical analyses were completed using SAS software, version 9.3 (SAS Institute, Cary, NC). Our study was exempt from review by the Human Subjects Committee of the University of Minnesota's Institutional Review Board because it used preexisting data with no personal identifiers.

Results

We identified 4765 patients diagnosed with appendiceal cancer from 2000–2009. The most common malignancies were mucinous adenocarcinoma (38 %), followed by carcinoid (28 %), adenocarcinoma-NOS (27 %), and signet ring cell adenocarcinoma (7 %). Both mucinous (51 %) and signet ring cell adenocarcinoma (60 %) patients were more likely to have distant disease at diagnosis, whereas the carcinoid and adenocarcinoma-NOS cohorts were proportionally less likely to have distant disease (15 and 25 %, respectively). The median age at diagnosis was 58 years for both men and women and remained stable over the study period.

Incidence Rates

Over the period 2000–2009, the overall incidence rate per 100,000 population steadily rose from 0.63 in 2000 to 0.97 in 2009, a 54 % increase (Fig. 1). Appendiceal cancer incidence rose in all four histology groupings and for all tumor stages. The smallest increase was in the unstaged cases (29 % increase) and the greatest increase in the localized cases (86 % increase). We found cancer rates increased across all age groups, both genders and all three racial/ethnic categories (Tables 1 and 2).

For all years except 2007, the rate of appendiceal cancer was higher in women than in men. For example, in 2009, the

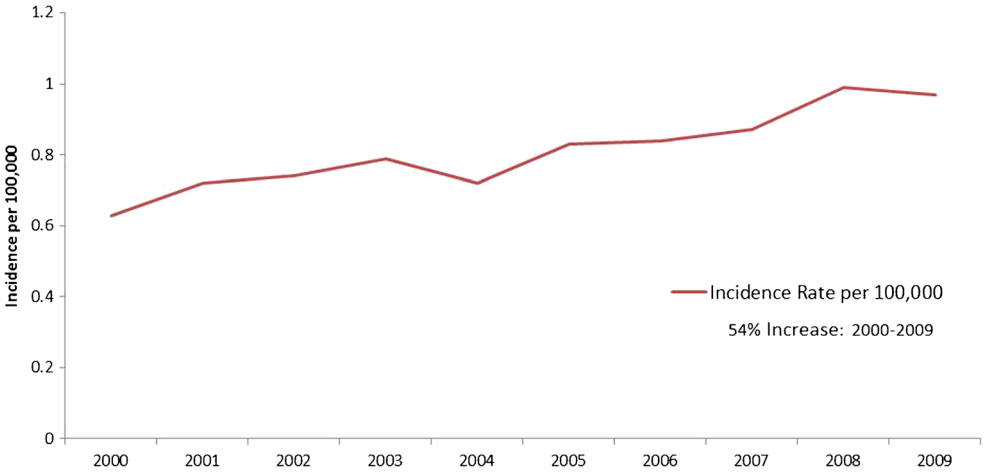

Fig. 1 Annual incidence of appendiceal cancer per 100,000; 2000–2009

rate in women was 1.01 per 100,000 and the rate in men was 0.92 per 100,000 population. The incidence of appendiceal cancer rose steadily with age peaking at 70 and older. The incidence of appendiceal cancer was highest in non-Hispanic whites and lowest in persons not classified as black or non-Hispanic white. Incidence rose in all years for all three racial/ethnic groupings (Tables 1 and 2).

By 2009, incidence was roughly equivalent for carcinoid (0.27 per 100,000), adenocarcinoma-NOS (0.29 per 100,000), and mucinous adenocarcinoma (0.33 per 100,000). Signet

Table 1 Incidence rate per 100,000 by patient characteristics and year: 2000-2009

		2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
	Total	0.63	0.72	0.74	0.79	0.72	0.83	0.84	0.87	0.99	0.97
Gender	Female	0.36	0.40	0.41	0.44	0.41	0.45	0.45	0.43	0.53	0.53
	Male	0.28	0.34	0.34	0.37	0.34	0.40	0.40	0.46	0.47	0.47
Patient age	18–39	0.07	0.08	0.1	0.08	0.07	0.09	0.09	0.07	0.09	0.09
	40–49	0.12	0.14	0.13	0.18	0.14	0.18	0.13	0.14	0.16	0.17
	50–59	0.14	0.16	0.18	0.19	0.19	0.21	0.23	0.24	0.28	0.24
	60–69	0.12	0.14	0.13	0.13	0.13	0.16	0.19	0.21	0.24	0.22
	70–79	0.13	0.13	0.13	0.13	0.12	0.12	0.13	0.14	0.14	0.16
	80–89+	0.05	0.07	0.07	0.09	0.06	0.07	0.07	0.07	0.08	0.1
Patient race	Non-Hispanic White	0.55	0.6	0.64	0.69	0.62	0.7	0.69	0.73	0.83	0.82
	Black	0.05	0.08	0.07	0.07	0.06	0.07	0.08	0.08	0.09	0.08
	Other	0.03	0.05	0.03	0.02	0.03	0.06	0.06	0.06	0.07	0.07
Cancer stage	Localized	0.22	0.28	0.3	0.26	0.28	0.35	0.33	0.34	0.37	
	Regional	0.15	0.15	0.17	0.21	0.18	0.19	0.19	0.23	0.24	0.23
	Distant	0.24	0.26	0.26	0.3	0.24	0.28	0.3	0.27	0.35	0.31
	Unstaged	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.03	0.02	0.02
Tumor Size	<1 cm	0.39	0.46	0.48	0.5	0.06	0.06	0.06	0.05	0.06	0.07
	1–1.9 cm	0.04	0.07	0.08	0.08	0.08	0.08	0.09	0.07	0.12	0.11
	2-4.9 cm	0.14	0.13	0.11	0.14	0.12	0.18	0.16	0.21	0.22	0.23
	5+ cm	0.06	0.07	0.08	0.08	0.12	0.13	0.14	0.13	0.16	0.16
	Unknown					0.34	0.39	0.38	0.41	0.42	0.4
Histology	Carcinoid	0.17	0.17	0.22	0.23	0.23	0.25	0.23	0.25	0.27	0.27
	Adenocarcinoma-NOS	0.19	0.22	0.19	0.19	0.22	0.19	0.19	0.23	0.23	0.29
	Mucinous adenocarcinoma	0.24	0.28	0.28	0.32	0.24	0.33	0.34	0.33	0.4	0.33
	Signet ring cell adenocarcinoma	0.03	0.05	0.05	0.05	0.04	0.06	0.07	0.05	0.08	0.08

Table 2 Basic patient and tumor characteristics by histology groups: 2000–2009

		Carcinoid		Adenocarcinoma-NOS		Mucinous adenocarcinoma		Signet ring cell adenocarcinoma		*P* value
		N	%	*N*	%	*N*	%	*N*	%	
Total		1339	28	1265	27	1822	38	339	7	
Diagnosis year	2000	94	7	106	8	132	7	18	5	0.0641
	2001	98	7	125	10	156	9	29	9	
	2002	124	9	109	9	163	9	30	9	
	2003	132	10	110	9	188	10	28	8	
	2004	132	10	126	10	138	8	25	7	
	2005	144	11	112	9	191	10	33	10	
	2006	137	10	116	9	205	11	42	12	
	2007	148	11	141	11	201	11	33	10	
	2008	164	12	142	11	246	14	49	14	
	2009	166	12	178	14	202	11	52	15	
Gender	Female	708	53	595	47	1020	56	219	65	<0.0001
	Male	631	47	670	53	802	44	120	35	
Patient age	18–39	244	18	82	6	145	8	13	4	<0.0001
	40–49	308	23	166	13	307	17	90	27	
	50–59	360	27	273	22	487	27	99	29	
	60–69	229	17	280	22	409	22	66	19	
	70–79	138	10	280	22	306	17	52	15	
	80–89+	60	1	184	4	168	4	19	0	
Patient race	Non-Hispanic White	1188	89	1023	81	1536	84	290	86	<0.0001
	Black	96	7	168	13	148	8	30	9	
	Other/unknown	55	4	74	6	138	8	19	6	
Cancer stage	Localized	743	55	556	44	490	27	64	19	<0.0001
	Regional	365	27	356	28	356	20	67	20	
	Distant	196	15	322	25	926	51	205	60	
	Unstaged	35	3	31	2	50	3	3	1	
Tumor size	<1 cm	418	31	299	24	464	25	71	21	<0.0001
	1–1.9 cm	235	18	124	10	104	6	17	5	
	2–4.9 cm	252	19	324	26	309	17	80	24	
	5+ cm	100	7	171	14	340	19	53	16	
	Unknown	334	25	347	27	605	33	118	35	

ring cell adenocarcinoma tumors were the least common with annual incidence of 0.08 per 100,000.

Stage of Disease at Diagnosis

Overall, 74 % of appendiceal cancer cases were diagnosed with either regional (39 %) or distant (35 %) metastases. Five-year survival rates were 77 % for persons diagnosed with local disease, 60 % for regional disease, and 33 % for distant disease. We sought to identify patient and tumor factors associated with distant disease at diagnosis. Both mucinous adenocarcinoma (51 %) and signet ring cell adenocarcinoma (60 %) histologies were more likely to have distant disease at diagnosis whereas carcinoid and adenocarcinoma-NOS histologies were proportionally less likely to have distant disease (15 and 25 %, respectively). Distant disease at diagnosis was more likely for women than for men (61 % vs. 39 %) and for those who were younger at diagnosis. Non-Hispanic whites were less likely to be diagnosed with distant disease than other races.

When we adjusted for histology, age, gender, race, diagnostic year, and registry, we found that the relative odds of distant disease was greatest for signet ring cell histology adenocarcinoma {adjusted odds ratio (OR) signet ring adenocarcinoma vs. carcinoid, 5.38; 95 % confidence interval (CI), 3.99–7.25} but also high for mucinous histology {adjusted OR mucinous vs. carcinoid, 3.53; 95 % CI, 3.01–4.13}. Race and diagnosis year were not significant factors for distant disease at diagnosis (Table 3). Men had lower odds of distant

Table 3 Relative odds of distant disease at diagnosis: 2000–2009

		OR	95 % CI	
Histology groups	Carcinoid	Ref		
	Adenocarcinoma-NOS	1.76	1.49	2.08
	Mucinous adenocarcinoma	3.53	3.01	4.13
	Signet ring cell adenocarcinoma	5.38	3.99	7.25
Patient age	18–39	Ref		
	40–49	1.29	1.01	1.63
	50–59	1.43	1.14	1.8
	60–69	1.27	1.01	1.61
	70–79	0.97	0.76	1.24
	80–89+	0.78	0.59	1.03
Gender	Female	Ref		
	Male	0.75	0.666	0.85
Patient race	Non-Hispanic White	Ref		
	Black	0.97	0.78	1.20
	Other/unknown	1.23	0.91	1.68
Diagnosis year	2000	Ref		
	2001	0.81	0.59	1.10
	2002	0.80	0.59	1.08
	2003	1.13	0.83	1.54
	2004	0.92	0.67	1.25
	2005	0.72	0.54	0.98
	2006	0.78	0.58	1.05
	2007	0.84	0.63	1.13
	2008	0.83	0.62	1.11
	2009	0.73	0.55	0.97

Adjusted for gender, histology group, age, race distributions, tumor size, stage, registry, year of diagnosis

disease at diagnosis than women. We also found that patient age (40 years old and older) was significantly associated with higher relative odds of distant disease at diagnosis.

Survival

The overall 5-year survival rates ranged from 82 % for carcinoid histology to 38 % for the signet ring cell adenocarcinoma (Fig. 2). After adjusting for histology, race, sex, age, diagnosis year, stage at diagnosis, tumor size, and registry, we found these survival differences remained. The highest hazards of death (relative to carcinoids) were observed in signet ring cell adenocarcinoma-NOS histologies {adjusted hazard ratio (HR), 2.11 and 1.49, respectively}. However, we found mucinous adenocarcinoma was associated with lower hazard of death relative to persons with carcinoid tumors {adjusted HR: 0.80 vs. carcinoid}. Older patient age, black race, larger tumor size, and distant disease at presentation were significantly associated with higher 5-year relative hazard of death ($P<0.05$ for all).

Discussion

We observed a striking 54 % increase in the incidence of appendiceal cancer in the USA over a 10-year period. This increase was observed consistently across age, gender, histology, and racial/ethnic groups. Thus, while rare, the population impact of appendiceal cancer may be increasing. We did not observe particular changes in patterns that would provide insights about the cause of this change. For example, while Misdraji et al. recommended the importance of differentiating between ovarian and appendiceal tumors[7], we observed increases for both men and women. Thus, reclassification of ovarian cancer to appendiceal cancer does not explain our observations. Likewise, while the use of colonoscopy increased during our study period[8], we found increases in age groups that are typically considered eligible for screening (e.g., age 50–59); however, we also observed increased incidence of appendiceal cancer among patients who are either too young (under age 40) or too old (age 80 and older) to undergo routine colorectal cancer screening. The lack of age-specific impact along with the lack of differential pattern by histology, stage at diagnosis, or tumor sizes leads to the conclusion that it is unlikely that increased use of colonoscopy would explain this trend. This conclusion is supported by the work of Trivedi et al. who notes that very few appendix tumors are found during colonoscopies.[9] Furthermore, the increased use of CT imaging during our study period[5] may contribute to the apparent increase in the incidence of appendiceal cancer. We cannot rule out the possibility that a variety of factors have combined to result in an apparent increase that is, in fact, merely a collection of small changes in detection rather than a true increase in incidence. Further work is needed to understand these trends and better determine the appropriate response (Table 4).

Other investigators have noted that appendiceal cancer is not typical of colorectal cancers.[10] Indeed, the median age at diagnosis of appendiceal cancer is 58 years in contrast to 72 years for colorectal cancer. The relatively young age at diagnosis is similar to that of ovarian cancer (63 years), cervical cancer (49 years), and anal cancer (60 years).[11] For women, the combination of patterns of regional spread, similar histologies, and age at diagnosis likely explains the often noted diagnostic confusion between ovarian cancer and appendiceal cancer. Sitzmann and Wiebke have recently

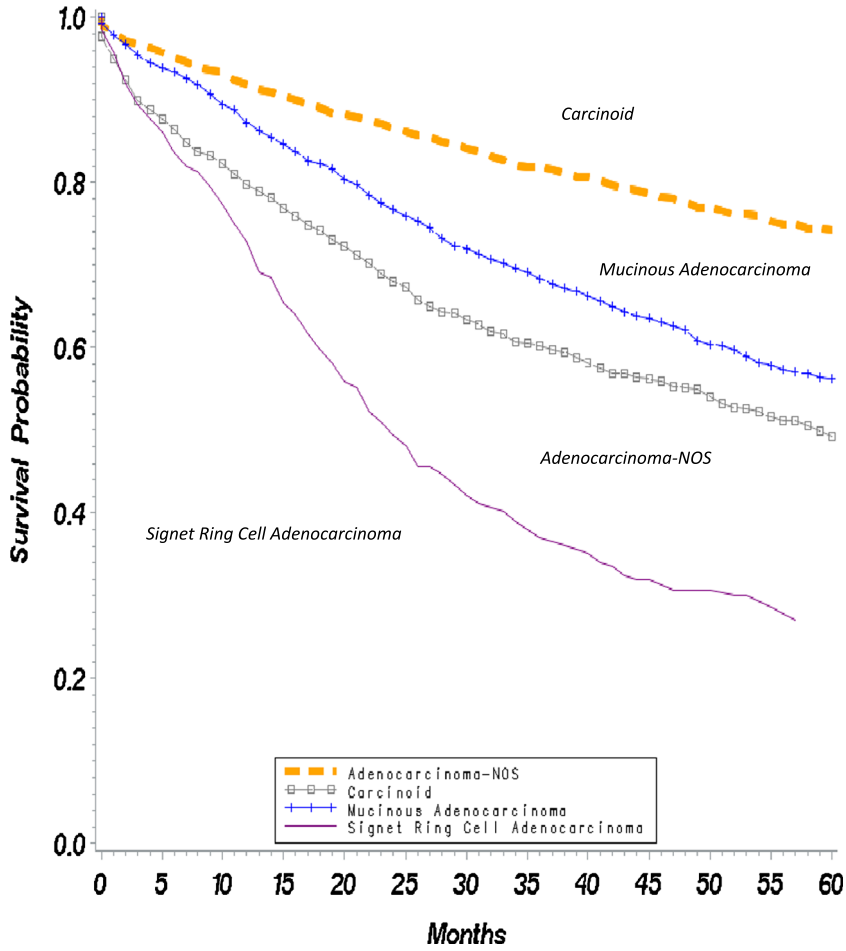

Fig. 2 Kaplan-Meier Curves of Appendiceal Cancer by Histology Group: 2000–2009

published a meta-analysis suggesting that perhaps some appendiceal cancer is associated with BRCA mutations.[12]

Appendiceal cancer is typical of many solid organ tumors with survival varying by stage at diagnosis. However, our data also indicate that even though these different tumors arise from the same organ, their individual characteristics vary considerably. Although we found that the most common malignancies of the appendix were mucinous adenocarcinoma and adenocarcinoma-NOS, we observed that carcinoids have significantly better outcomes than the other three histology groups. As compared with pure carcinoid tumors, signet ring cell adenocarcinoma and adenocarcinoma-NOS are more aggressive neoplasms.[13–15] We found that the odds of distant disease at diagnosis were higher for the signet ring cell adenocarcinoma and mucinous adenocarcinomas.

We observed that overall survival is associated with the histology of appendiceal cancer patients. Unlike prior studies, we also identified an increase in overall incidence among each of the histology groups. Compared to the previous studies, we observed an older carcinoid (mean age: 53 years) and signet ring cell adenocarcinoma (mean age: 58 years) population and a higher proportion non-Hispanic whites in all histology categories.[1,3] We did not see increases differentially associated with stage, histology, registry, or demographic characteristics. Given renewed interest in orphan cancers, our findings support the idea that further investigation is needed to identify causal relationships in order to abate any further rise in incidence.

The current study has several SEER-related potential limitations. First, we cannot assess the role of misdiagnosis or whether the patient was diagnosed based on symptoms, or on routine screening or imaging. Detailed patient and tumor information that may have influenced treatment decisions were not available from the cancer registry database. Because SEER classifies tumor location based on ICD-O3 topography codes, we could not assess the association between tumor location within the appendix (i.e., base vs. tip) since only one topography code (18.1) is used for appendix tumors. Finally, SEER cancer registries do not collect information on several commonly cited prognostic factors in patients with gastrointestinal malignancies, such as patients' performance status, nutritional status, co-morbidities, surgeon, and hospital volume.[16–18] Despite these potential limitations, SEER

Table 4 Factors associated with 5-year relative hazard of death among appendiceal cancer patients, Cox proportional hazard models, hazard ratio, and 95 % CI

		Hazard ratio	95 % CI		*P* value
Histology groups	Carcinoid	Ref			
	Adenocarcinoma-NOS	1.46	1.26	1.7	<0.0001
	Mucinous adenocarcinoma	0.78	0.67	0.91	0.002
	Signet ring cell adenocarcinoma	2.06	1.71	2.49	<0.0001
Gender	Female	Ref			
	Male	1.1	1.001	1.22	0.0468
Patient age	18–39	Ref			
	40–49	1.48	1.15	1.91	0.002
	50–59	1.78	1.4	2.26	<0.0001
	60–69	2.04	1.6	2.6	<0.0001
	70–79	2.89	2.27	3.69	<0.0001
	80–89+	5.35	4.15	6.9	<0.0001
Patient race	Non-Hispanic White	Ref			
	Black	1.22	1.04	1.45	0.01
	Other/unknown	1.01	0.86	1.16	0.95
Tumor size	<1 cm	Ref			
	1–1.9 cm	1.04	0.74	1.46	0.79
	2–4.9 cm	1.28	0.94	1.72	0.1
	5+ cm	1.56	1.15	2.11	0.004
	Missing	1.34	1.01	1.79	0.04
Cancer stage	Localized	Ref			
	Regional	1.82	1.571	2.116	<0.0001
	Distant	4.82	4.21	5.526	<0.0001
	Unstaged	1.98	1.405	2.798	<0.0001
Diagnosis year	2000	Ref			
	2001	0.87	0.72	1.06	0.17
	2002	0.87	0.71	1.05	0.16
	2003	0.94	0.78	1.14	0.58
	2004	0.89	0.72	1.09	0.28
	2005	0.8	0.65	0.99	0.04
	2006	0.85	0.69	1.05	0.14
	2007	0.71	0.57	0.9	0.01
	2008	0.78	0.61	1.01	0.05
	2009	0.81	0.58	1.13	0.21

Adjusted for gender, histology group, age, race distributions, tumor size, stage, registry, year of diagnosis

is a robust population database and accurately reflects cancer treatment trends in the USA.

Conclusion

In conclusion, although appendiceal cancer is rare, the incidence increased significantly in the USA from 2000 to 2009. Although we did not observe an obvious cause for these trends, the increased use of CT scanning may have contributed to the findings. The observation that both carcinoid and adenocarcinoma are increasing supports the idea that these observations may be partially due to increased detection of asymptomatic patients. However, we also found that the incidence of appendiceal cancer with distant metastases increased during the study period. Therefore, it is unlikely that the observed trends are entirely due to increased detection. We are unaware of environmental reasons that would explain the increase in these disparate tumor types. We did not see increases differentially associated with stage, histology, registry, or demographic characteristics. Further investigation is needed to examine factors underlying this increase.

Funding for this study This research was generously supported by the Betti Boers Maloney Appendiceal Cancer Research Fund at the University of Minnesota Foundation

Conflicts of interest No financial disclosures/conflicts of interest.

Appendix

Stepwise Ascertainment of Final Pool of Patients

- Start: Appendiceal cancer cases diagnoses 2000–2009 (code 8013, 8240, 8241, 8243, 8244, 8245, 8246, 8249, 8574, 8140, 8144, 8210, 8211, 8220, 8255, 8260, 8261, 8262, 8263, 8440, 8000, 8010, 8470, 8471, 8480, 8481, 8490): 4876
- After excluding cases diagnosed in a nursing home, by autopsy, or on death certificate: 4839
- After excluding in situ cases and cases without microscopic confirmation: 4768
- After excluding cases from Alaska and Rural Georgia (<5 cases): 4765

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