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ORIGINAL ARTICLE

Elevated risk of subsequent malignancies in patients with appendiceal cancer: A population-based analysis

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Abstract
Background Appendiceal cancer is extremely rare with excellent survival after curative resection. There is a concern for the development of additional cancers in survivors of appendiceal cancer. However, existing data is limited to small anecdotal reports on appendiceal carcinoid only. We aim to investigate the risk of subsequent malignancies in patients with appendiceal carcinoma and correlate the risk according to patient and clinical characteristics.
Methods We identified 3788 patients with appendiceal cancer from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database between 1992 and 2011. Standardized incidence ratios (SIRs) for the risk of additional cancers were calculated and quantified based on tumor site, gender, race, latency, primary tumor stage, and histology.
Results Three hundred and fifty-nine subsequent malignancies were identified in 313 patients (mean age 60 years, male to female ratio 1.3:1). The overall risk for a subsequent malignancy was elevated by 20 % compared with the general population. Most common sites with significantly increased risk for subsequent cancers included the small intestine (n=13) and the colon/rectum (n=48). Malignant carcinoid and adenocarcinoma were the dominant histological subtypes at these sites, respectively. Significant elevated risk was observed within the first 5 years of follow up in white males with either localized or regional disease. Adenocarcinomas and goblet cell carcinoid tumors of the appendix were associated with increased risk; whereas, the risk was significantly reduced in patients with malignant carcinoid tumors.
Conclusion There is an increased risk of subsequent cancers in patients with appendiceal carcinoma.

Keywords Additional tumors · Appendiceal cancer · Second malignancy · SEER

Introduction

Appendiceal carcinomas (AC) are extremely rare, accounting for approximately 0.5 % of all intestinal tumors [1]. Our knowledge about appendiceal tumors is based mainly on anecdotal reports with a small number of cases. The majority of appendiceal cancers are discovered incidentally in appendectomy specimens, and further surgical management is subject to debate. However, evidence from literature and consensus-based guidelines advocate complete right colectomy for patients with tumors greater than 2 cm and for tumors <2 cm and presence of meso-appendiceal invasion or adverse histological features [2, 3].

Currently, there are no evidence-based guidelines for follow up after resection for appendiceal cancer. Generally, no follow up is advised for tumors <2 cm and treated by simple appendectomy [4]. Although some histological variants such as signet ring cell carcinoma are associated with poor prognosis, the overall survival of patients with appendiceal cancer is excellent. For instance, 5-year survival rate of appendiceal carcinoid <3 cm without regional nodal or distant metastases is reported to be 100 % [5].

It is well established that cancer survivors are prone to developing additional subsequent cancers [6]. However,

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despite growing knowledge on the occurrence of additional cancers in patients with other malignancies [7, 8], data is insufficient for appendiceal cancer. There is limited evidence from small retrospective series suggesting an elevated risk of additional malignancies in patients successfully treated for carcinoid tumors of the appendix [9]. However, except for carcinoid tumors, the risk of additional malignancies in other histological subtypes has not been explored. Considering a high 5-year survival rate after surgical resection, there exists a need to report occurrence of additional subsequent cancers among survivors of appendiceal cancer.

In this work, we aim to investigate the risk of subsequent malignancies in patients with appendicular carcinoma compared to the general population, including an analysis on whether several demographic and clinical characteristics are associated with having a higher or a lower risk of these subsequent cancers.

Methods

National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database was utilized for data mining. SEER database is a set of 18 cancer registries that covers approximately 28 % of the US population. We used SEER 13 Regs Research Data, Nov 2013 Sub (1992–2011) database [10] and identified cases with histologically confirmed appendiceal carcinoma from 1992 to 2011 using site code for appendix (C18.1). We only included patients who were surgically treated for AC. Patients with unknown or missing variable status on demographics, tumor characteristics, and treatment were excluded. In addition, subsequent malignant neoplasms (SMNs) diagnosed during the 2-month period after the primary diagnosis of AC were excluded due to potential misclassification of synchronous cancers and metastases. Patient selection algorithm is shown in Fig. 1.

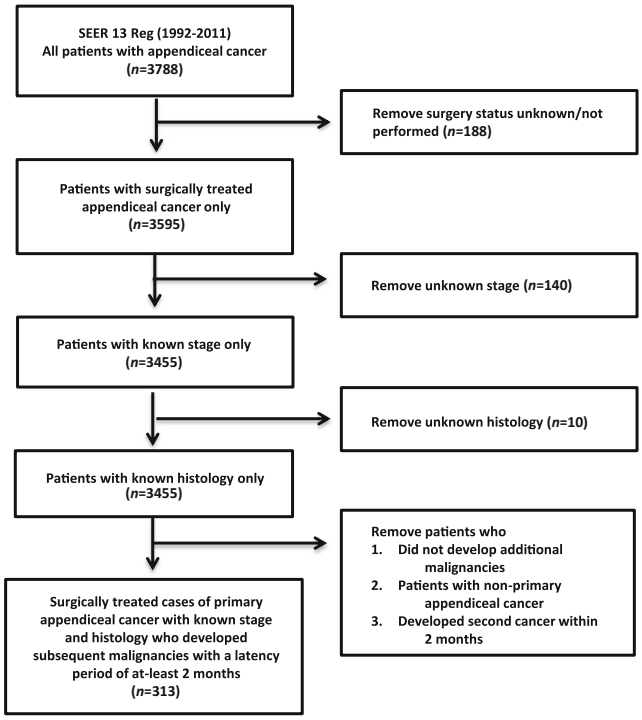

Fig. 1 Patient selection algorithm

Statistical analysis

We used the multiple primary standardized incidence ratio session of SEER stat software. Standardized incidence ratio (SIRs) were used to estimate the risk of additional neoplasms after AC. SIRs is defined as the number of observed cases divided by the number of expected cases of additional cancer. The 2000 US Standard Population was used as the reference population in the determination of the expected incidence. Confidence intervals were calculated using the Poisson distribution assumption [8, 11].

Subgroups analysis for expected incidence rates were stratified by gender, race (white, black, others), latency period (2–11 months, 12–59 months, >60 months), primary tumor stage (localized, regional, distant), and primary tumor histology. Tumor histology was consolidated into five groups using International Classification of Disease (ICD) oncology codes and based on similar histopathological and clinical features as defined previously [12]. The groups consisted of malignant carcinoid, goblet cell carcinoid, adenocarcinoma, mucinous adenocarcinoma, and signet ring cell adenocarcinoma. Disease stage was derived from SEER Historic Stage variable and included three categories. Tumors limited to the site of origin were coded as "Localized" disease; extension beyond the primary organ into the surrounding structure, lymph nodes, or combination was categorized as "Regional" malignancies. Distant metastasis was coded as "Distant."

Differences between groups were assessed using χ^2 tests for categorical variables and Student's t test for continuous variables. A multivariate analysis using the Cox-proportional hazards model was used to evaluate the association between various factors and the development of subsequent malignant cancers. Analysis was conducted using SEER stat software version 8.2.1 (available at: http://seer.cancer.gov/seerstat/; release April 8, 2015) and Statistical Package for the Social Sciences (SPSS v.22) Software. A p-value of ≤ 0.05 was considered as statistically significant.

Results

Patient characteristics

Among 3445 patients with surgically treated primary appendiceal cancer, 313 (9.1 %) developed 359 subsequent

Table 1 Characteristics of patients with surgically treated primary appendiceal cancer (*n*=3445)

Subsequent cancer			
Variable	Yes (*n*=313)	No (*n*=3132)	*p*-value
Age at diagnosis (SD), years	60 (13.7)	54 (16.9)	<0.001
Mean follow up, months	133	91	<0.001
Gender (%)			<0.001
Male	179 (57.2)	1457 (56.6)	
Female	134 (42.8)	1675 (53.5)	
Race (%)			0.884
White	263 (84.0)	2646 (84.5)	
Black	29 (9.3)	266 (8.5)	
Others (American Indian/Asian/Pacific Islander)	21 (6.7)	220 (7.0)	
Primary tumor histology (%)			0.002
Malignant carcinoid	34 (10.9)	489 (15.6)	
Goblet cell carcinoid	73 (23.4)	667 (21.3)	
Adenocarcinoma	101 (32.4)	746 (23.9)	
Mucinous adenocarcinoma	94 (30.1)	1040 (33.3)	
Signet ring cell adenocarcinoma	10 (3.2)	183 (5.9)	
Stage of primary cancer (%)			<0.001
Localized	176 (56.2)	1351 (43.1)	
Regional	95 (30.4)	827 (26.4%)	
Distant	42 (13.4)	954 (30.5)	

malignancies. Mean age at diagnosis of primary appendiceal cancer was 60 years with a male predominance (57 %). Adenocarcinoma (32.4 %) was the most prevalent subtype of primary appendiceal cancer, followed by mucinous adenocarcinoma (30 %) and goblet cell carcinoid (23 %). The stage of primary appendiceal cancer was localized (56.2 %) in the majority of patients. Primary tumor characteristics for patients who developed additional malignancies and patients with no subsequent cancers are summarized in Table 1.

Overall risk by cancer site, gender, and race

The overall risk for a subsequent malignancy at all sites was elevated by 20 % compared with the general population (SIR,

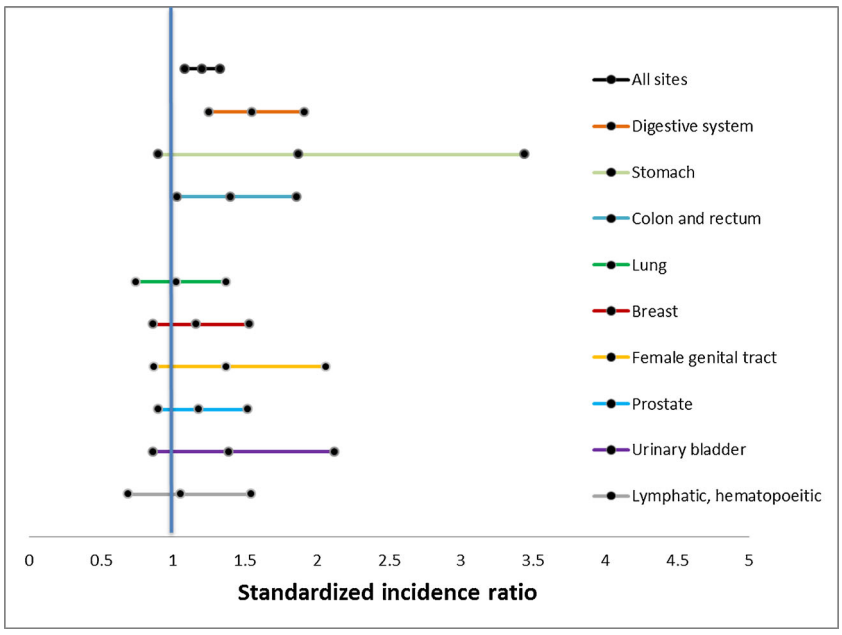

Fig. 2 The standardized incidence ratios for the risk of additional cancers in patients with appendiceal cancer

Table 2 Standardized incidence ratios of second cancer risk in patients with appendiceal cancer, overall, and by sex

Location of subsequent cancer	Total		Men		Women	
	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)
All sites	359	1.20 (1.08–1.33)[a]	201	1.24 (1.08–1.42)[a]	158	1.14 (0.97–1.34)
Oral cavity	9	1.29 (0.59–2.46)	5	1.06 (0.34–2.48)	4	1.78 (0.49–4.57)
Digestive system	91	1.55 (1.25–1.91)[a]	58	1.80 (1.36–2.32)[a]	33	1.26 (0.86–1.76)
Esophagus	6	1.92 (0.70–4.17)	5	2.10 (0.68–4.90)	1	1.33 (0.03–7.43)
Stomach	10	1.87 (0.90–3.44)	6	1.75 (0.64–3.81)	4	2.08 (0.57–5.33)
Small intestine	13	10.59 (5.64–18.11)[a]	10	15.13 (7.25–27.83)[a]	3	5.30 (1.09–15.48)[a]
Colon and rectum	48	1.40 (1.03–1.86)[a]	32	1.79 (1.22–2.52)[a]	16	0.98 (0.56–1.59)
Lung	44	1.02 (0.74–1.37)	28	1.13 (0.75–1.64)	16	0.87 (1.49–1.41)
Skin	9	0.74 (0.34–1.41)	6	0.83 (0.31–1.81)	3	0.61 (0.13–1.77)
Breast	49	1.16 (0.86–1.53)	1	2.93 (0.07–16.30)	48	1.14 (0.84–1.52)
Female genital system	23	1.37 (0.87–2.06)	–	–	23	1.37 (0.87–2.06)
Prostate	59	1.18 (0.90–1.52)	59	1.18 (0.90–1.52)	–	–
Kidney	7	0.95 (0.38–1.95)	2	0.43 (0.05–1.56)	5	1.81 (0.59–4.23)
Urinary bladder	21	1.39 (0.86–2.12)	17	1.46 (0.85–2.34)	4	1.14 (0.31–2.91)
Lymphatic hematopoietic	26	1.05 (0.69–1.54)	15	1.09 (0.61–1.79)	11	1.01 (0.50–1.80)
Miscellaneous	21	–	–	–	–	–

CI confidence interval, *SIR* standardized incidence ratio

[a] $p < 0.05$

1.20; 95 % CI, 1.08–1.33, $p < 0.05$). A significant excess risk of subsequent cancers was observed in the small intestine (SIR, 10.59; 95 % CI, 5.64–18.11) followed by the colon/rectum (SIR, 1.40; 95 % CI, 1.03–1.86) (Fig. 2). Malignant carcinoid and adenocarcinoma were the dominant histological subtypes of subsequent cancers at these sites, respectively. A large numbers of additional malignancies were observed in the prostate ($n = 59$), the breast ($n = 49$), and the lung ($n = 44$), but the risk was not significantly increased as compared to the general population.

Notable differences were observed between various demographic and clinical characteristics and the probability of developing additional malignancies. When stratified by gender and race, the risk of additional malignancies at all sites was significant in men (SIR, 1.24; 95 % CI, 1.08–1.42) with white (SIR, 1.17; 95 % CI, 1.04–1.31) or other (American Indian/Asian/Pacific Islander) races (SIR, 1.66; 95 % CI, 1.04–2.52). No significant elevated risk was observed in females and in the black race. Overall SIRs by site and gender are summarized in Tables 2 and 3.

SIRs according to follow up time after appendiceal cancer diagnosis

SIRs according to latency period were calculated for selected cancer sites with statistically significant elevated cancer risk.

Table 3 Standardized incidence ratios of selected second cancers by race

Location of cancer	Race					
	White		Black		Others (American Indian/Asian/Pacific Islander)	
	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)
All sites	305	1.17 (1.04–1.31)[a]	32	1.35 (0.92–1.90)	22	1.66 (1.04–2.52)[a]
Digestive system	73	1.49 (1.17–1.87)[a]	10	1.88 (0.90–3.46)	8	2.05 (0.88–4.03)
Small intestine	11	10.68 (5.33–19.11)[a]	1	6.86 (0.17–38.24)	1	22.01 (0.56–122.65)
Colon and rectum	39	1.33 (0.95–1.82)	5	1.76 (0.57–4.12)	4	2.13 (0.58–5.44)

CI confidence interval, *SIR* standardized incidence ratio

[a] $p < 0.05$

Table 4 Standardized incidence ratios of selected second cancers by latency period

Location of cancer	Latency period					
	2–11 months		12–59 months		≥60 months	
	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)	No. of cancers	SIR (95 % CI)
All sites	51	1.91 (1.43–2.52)[a]	136	1.54 (1.29–1.82)[a]	172	0.93 (0.80–1.08)
Digestive system	18	3.43 (2.03–5.43)[a]	35	2.02 (1.40–2.80)[a]	38	1.06 (0.75–1.45)
Small intestine	2	18.59 (2.25–67.14)[a]	5	14.05 (4.56–32.78)[a]	6	7.85 (2.88–17.09)[a]
Colon and rectum	13	4.24 (2.26–7.25)[a]	17	1.86 (0.98–2.69)	18	0.85 (0.51–1.35)

CI confidence interval, *SIR* standardized incidence ratio

[a] $p < 0.05$

We found that the risk of additional tumors was most evident within the first 5 years after the diagnosis of primary appendiceal cancer. The greatest risk was seen within 1 year (SIR, 1.91; 95 % CI, 1.43–2.53). The increased risk of subsequent cancers normalized after 5 years of follow up (Table 4).

SIRs according to primary tumor stage and histology

SIRs according to primary tumor stage and histology were calculated for all tumor sites. Increased risk of subsequent malignancies was observed for localized (SIR, 1.16; 95 % CI, 1.00–1.33) and regional disease (SIR, 1.34; 95 % CI, 1.10–1.61). No statistically significant risk was seen with distant disease (Fig. 3) possibly reinforcing the lower survival rates of advanced disease. Based on histological subtypes of appendiceal cancer, the greatest risk of additional cancer was observed with goblet cell carcinoid (SIR, 1.55; 95 % CI, 1.23–1.92) and adenocarcinoma (SIR, 1.42; 95 % CI, 1.18–1.69. The risk was significantly reduced in patients with malignant carcinoid tumor (Fig. 4).

In a multivariate Cox-proportional hazards model, increased age at diagnosis ($p<0.001$), male sex ($p<0.001$), and tumor histology (goblet cell carcinoid, adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma [$p<0.001$]) was associated with increased hazards of developing an additional malignancy, while race and disease stage had no significant effect on development of a subsequent cancer (Table 5).

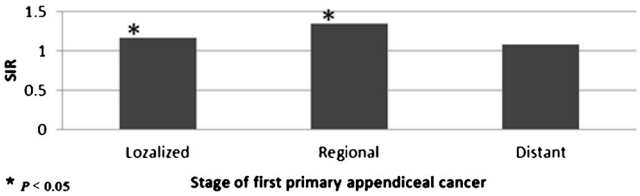

Fig. 3 SIR of additional cancer by stage of primary appendiceal cancer

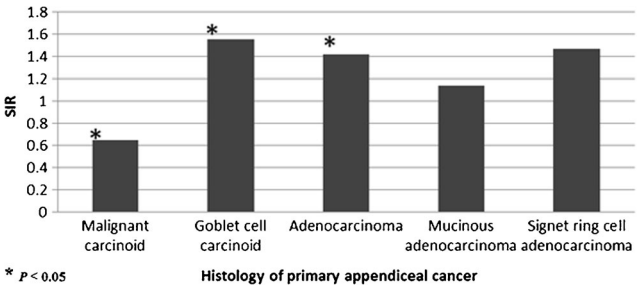

Fig. 4 Standardized incidence ratio of additional cancer by histology of primary appendiceal cancer

Discussion

We conducted a population-based analysis including patients with surgically treated primary appendicular cancer and ob-

Table 5 Multivariate Cox-regression model for the risk of additional subsequent malignancies in patients with primary appendiceal cancer

Variable	Hazard ratio (95 % CI)	*p*-value
Age at diagnosis	1.05 (1.04–1.06)	<0.001
Gender		<0.001
Female	(reference)	
Male	1.59 (1.26–2.00)	
Race		0.269
Others (American Indian/Asian/Pacific Islander)	(reference)	
Black	1.11 (0.71–1.74)	
White	1.50 (0.85–2.64)	
Disease stage		0.217
Localized	(reference)	
Regional	1.22 (0.95–1.58)	
Distant	1.26 (0.87–1.82)	
Tumor histology		<0.001
Malignant carcinoid	(reference)	
Goblet cell carcinoid	3.26 (2.05–5.20)	
Adenocarcinoma	2.55 (1.61–4.04)	
Mucinous adenocarcinoma	2.05 (1.29–3.26)	
Signet ring cell carcinoma	4.23 (2.00–8.97)	

served that 9.1 % developed additional subsequent malignancies, representing a 20 % excess risk compared to the general population. Small intestine and colorectal cancers accounted for the greatest significant cancer burden. Additional malignancies were primarily seen in males with white/Asian/Pacific Islander race. In patients with goblet cell carcinoids and adenocarcinomas of the appendix, the risk of developing an additional subsequent malignancy was elevated as compared to other histological subtypes. A multivariate Cox-regression model reinforced that increasing age at primary cancer diagnosis, male sex, and tumor histology was associated with increased hazards of developing an additional cancer.

With the increasing survival rates among cancer survivors, improved understanding and identification of long-term complications are important to guide surveillance, prevention and treatment. There is a scarcity of data on additional cancers after appendiceal carcinoma. Fernandez et al. [9] evaluated clinical course and follow up of 28 pediatric patients with an appendiceal carcinoid tumor. In a median follow up of 84 months, they observed no second malignancies. In contrast, Habal et al. [13] reviewed over 5000 cases of adult gastrointestinal carcinoids and reported a 13 % to 32 % rate of additional cancers in patients with appendiceal carcinoids. Similar to what we found in our analysis, adenocarcinoma of the colon was the most common subsequent malignancy observed in their review. Interestingly, all previous reports have investigated the risk in appendiceal carcinoids only which were previously believed to be the most common histological subtype at this site. However, recent literature [12] reports mucinous adenocarcinoma to be the most appendiceal tumor followed by intestinal-type adenocarcinoma, with carcinoid tumors comprising only 11 % of all appendiceal tumors.

To the best of our knowledge, this is the first population-based study with the largest number of patients that reports the occurrence of additional malignancies after primary appendiceal cancer. We highlight the possibility of additional malignancies specific to anatomic sites, latency, and various demographic and primary tumor characteristics. The main strengths of our study were its large sample size, an inclusion of all appendiceal cancer histologies, and long-term follow up. The larger sample size of our study was important for increasing the precision of results for studying associations. Additionally, utilization of a population-based database provided us with a high level of quality control and reflects national patterns with increasing generalizability of our results. Furthermore, we quantified our results based on several patient and clinical characteristics with the risk of developing additional cancer and identified the population at risk. Moreover, we only included cases with a primary diagnosis of appendiceal cancer, thus, eliminating the potential confounding of other malignancies on the development of additional cancers.

There are limitations to consider with the present study. SEER database lacks information on comorbidities, risk factors, family history of cancer, occupation, genetic mutations, and the use of chemotherapy. In addition, the inherent limitations of its retrospective nature and using a population-based database including reporting errors, misdiagnosis, and miscoding, exist in this study. Another potential limitation is the lack of classification of subsequent cancer as recurrence vs. a new primary. It is possible that some tumor recurrences may be misclassified as a new primary tumor. We cannot deny the effect of detection bias which might reflect a higher incidence of subsequent digestive tract malignancies in our sample. Despite all these limitations, this is the largest group of cohort reported to date and the first study that investigated additional cancer risk after appendiceal cancer.

Our study reports a 20 % increased risk of subsequent cancers in patients with appendicular carcinoma compared to the general population. The risk of additional tumors was most evident within the first 5 years of follow up in males with adenocarcinoma or goblet cell carcinoid of the appendix. This warrants for increased early surveillance in patients who are considered to be cured after resection for primary appendiceal cancer.

Compliance with ethical standards

Conflict of interest AA, OP, NS-R, WR, and FYB declare that they have no conflict of interest.

Ethics statement The authors declare that the study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and the authors followed the policy concerning Informed consent as shown on Springer.com.

References

1. Hesketh KT. The management of primary adenocarcinoma of the vermiform appendix. Gut. 1963;4:158–68.
2. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. N Engl J Med. 1987;317:1699–701.
3. Pape UF, Perren A, Niederle B, et al. ENETS consensus guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology. 2012;95:135–56.
4. Adil SR, Meyerhardt JA. Cancer of the appendix and pseudomyxoma peritonei. In: UpToDate, Tanabe KK (Ed), UpToDate, Waltham, MA. Accessed 23 March 2016.

5. Landry CS, Woodall C, Scoggins CR, McMasters KM, Martin RC 2nd. Analysis of 900 appendiceal carcinoid tumors for a proposed predictive staging system. Arch Surg. 2008;143:664–70 .discussion 670
6. Morton LM, Onel K, Curtis RE, Hungate EA, Armstrong GT. The rising incidence of second cancers: patterns of occurrence and identification of risk factors for children and adults. American Society of Clinical Oncology educational book / ASCO. American Society of Clinical Oncology. Meeting. 2014:e57–67.
7. Brunner AM, Hobbs G, Jalbut MM, Neuberg DS, Fathi AT. A population-based analysis of second malignancies among patients with myeloproliferative neoplasms in the SEER database. Leuk Lymphoma. 2016;57:1197–200.
8. Lee JS, DuBois SG, Coccia PF, Bleyer A, Olin RL, Goldsby RE. Increased risk of second malignant neoplasms in adolescents and young adults with cancer. Cancer. 2016;122:116–23.
9. Fernandez KS, Aldrink JH, Ranalli M, Ruymann FB, Caniano DA. Carcinoid tumors in children and adolescents: risk for second malignancies. J Pediatr Hematol Oncol. 2015;37:150–3.
10. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2014 Sub (1973–2012) < Katrina/Rita Population Adjustment > − Linked To County Attributes - Total U.S., 1969–2013 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2015, based on the November 2014 submission.
11. Tamboli D, Topham A, Singh N, Singh AD. Retinoblastoma: a SEER dataset evaluation for treatment patterns, survival, and second malignant neoplasms. Am J Ophthalmol. 2015;160:953–8.
12. Turaga KK, Pappas SG, Gamblin T. Importance of histologic subtype in the staging of appendiceal tumors. Ann Surg Oncol. 2012;19:1379–85.
13. Habal N, Sims C, Bilchik AJ. Gastrointestinal carcinoid tumors and second primary malignancies. J Surg Oncol. 2000;75:310–6.