

RESEARCH ARTICLE

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Second Primary Malignancies After Appendiceal Neuroendocrine Tumors: A Contemporary SEER-Based Standardized Incidence Ratio Analysis (2015–2023)

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Abstract

Background: Whether contemporary appendiceal neuroendocrine tumor (NET) survivors have an increased risk of second primary malignancies (SPMs) remains uncertain. We assessed relative incidence and the effect of excluding early post-diagnosis events. **Methods:** We identified adults aged ≥ 20 years with malignant appendiceal NETs diagnosed between 2015 and 2023 in Surveillance, Epidemiology, and End Results (SEER) data from 17 registries. Observed and expected SPMs were compared using standardized incidence ratios (SIRs). The primary analysis excluded events occurring within the first two months, with sensitivity analyses using ≥ 6 - and ≥ 12 -month exclusion periods. **Results:** The baseline cohort included 4,854 patients. At ≥ 2 months, 4,522 patients contributed 18,273.65 person-years, with 119 observed SPMs compared with 103.03 expected SPMs (SIR, 1.15; 95% CI, 0.96–1.38). Elevated estimates were observed for malignancies of the digestive system (SIR, 1.56; 95% CI, 1.03–2.27), pancreas (2.51; 1.01–5.17), kidney and renal pelvis (2.36; 1.08–4.49), and thyroid (2.73; 1.36–4.89). Overall SIRs were 1.15, 1.10, and 1.03 across the three exclusion thresholds. Several site-specific estimates decreased, but pancreatic SIRs remained similar (2.51, 2.70, and 2.58). No site-specific confidence interval excluded unity at ≥ 12 months. **Conclusions:** Overall SPM incidence was not significantly elevated. Early site-specific findings warrant caution because of small event counts, multiple comparisons, and possible detection effects that SEER cannot directly measure. Loss of statistical significance with longer exclusion periods does not exclude persistent site-specific excess incidence. These results do not support additional routine organ-directed screening solely based on appendiceal NET history.

Keywords: Cancer Survivors, Registries, Public Health Surveillance, Overdiagnosis, Follow-Up Studies

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Introduction

The clinical profile of neuroendocrine tumors (NETs) has changed considerably over the past two decades. Population-based studies show that NETs are being diagnosed more often, with a growing proportion identified at earlier stages and with improved long-term survival [1-3]. This shift has expanded the focus of care beyond initial tumor control. For many patients with well-differentiated NETs, survivorship issues, including the possibility of second primary malignancies (SPMs), have become increasingly relevant.

Appendiceal NETs occupy a distinct place within this broader NET landscape. They are frequently detected incidentally after appendectomy, often occur in relatively young patients, and are usually small, localized, and biologically indolent at diagnosis [4-7]. Contemporary guidelines reflect this favorable behavior: appendectomy alone is considered adequate for many small, well-differentiated tumors, while more extensive surgery or follow-up is generally reserved for selected

patients with higher-risk features [8-10]. Given the generally favorable prognosis of localized, well-differentiated appendiceal NETs, the long-term clinical question is not limited to recurrence or NET-related death. It also includes whether these survivors carry an excess risk of subsequent malignancy that should alter routine cancer screening or follow-up practice.

Several studies have examined SPMs after NETs or broader neuroendocrine neoplasms. The closest prior SEER-based analysis reported an increased burden of second primary cancers among NET survivors and showed that risk varied by the primary NET site [11]. Other registry-based studies have also described excess SPM risk after neuroendocrine neoplasms, with signals involving organs such as the colon, lung, kidney, prostate, pancreas, and thyroid [12-16]. These studies provide important context, but their findings are not automatically applicable to appendiceal NETs. Prior analyses often combined different primary sites, histologic categories, stages, and calendar eras. Appendiceal NETs differ from pancreatic, pulmonary, colorectal, gastric, and high-grade

neuroendocrine neoplasms in age distribution, route of diagnosis, tumor biology, and competing mortality risk.

The timing of SPM detection is also important. Malignancies diagnosed soon after an index cancer may represent a true shared predisposition, but they may also reflect increased diagnostic contact, staging investigations, abdominal imaging, endoscopy, or heightened clinical attention. Population-based work has shown that SPM estimates may change substantially when early post-diagnosis intervals are excluded [17]. This issue is particularly relevant for appendiceal NETs, where diagnosis often follows an acute surgical presentation and may be accompanied by additional evaluation. Therefore, latency-sensitive analyses are needed before early site-specific SPM signals are interpreted as durable excess cancer risk.

Whether findings from broader NET cohorts apply to contemporary, histologically defined appendiceal NETs, and whether site-specific signals persist after excluding early events, remains uncertain. We therefore compared observed and expected second primary malignancies in adults diagnosed during 2015–2023 and repeated the analyses using progressively longer latency exclusions.

Materials and Methods

Study Design and Data Source

We conducted a retrospective, population-based cohort study using the SEER Research Plus database, November 2025 submission, released in April 2026 (17 registries excluding Alaska, 2000–2023) [18]. We evaluated second primary malignancies with the SEER*Stat multiple primary standardized incidence ratio (MP-SIR) module [19]. We restricted index diagnoses to 2015–2023 to characterize a contemporary appendiceal NET cohort.

Cohort Definition

Eligible patients were adults aged 20 years or older with malignant appendiceal NET diagnosed between 2015 and 2023. Appendiceal NET was defined by primary site C18.1 and ICD-O-3 histology codes 8240/3, 8241/3, or 8249/3. Only patients for whom appendiceal NET was recorded as the only malignant primary or the first of two or more malignant primaries were included, ensuring that the index appendiceal NET preceded any subsequent malignancy. Patients with non-malignant behavior, histologies outside the prespecified NET codes, age younger than 20 years, diagnoses outside the study period, or death certificate-only/autopsy-only ascertainment were excluded. The final baseline cohort included 4,854 patients.

Definition and Ascertainment of Second Primary Malignancies

A second primary malignancy was defined and ascertained using the SEER program's multiple-primary coding rules, which determine whether a subsequent tumor is registered as an independent primary rather than a recurrence or metastasis of the index appendiceal NET. Only malignant tumors recorded after the index appendiceal NET were counted as second primaries, and person-time contributing to the observed-versus-expected

comparison accrued from the end of the applied latency-exclusion interval. Tumors registered within the excluded latency window were not counted as second primaries in the corresponding analysis.

Study Variables

Baseline and clinical variables included age at diagnosis, sex, race, year of diagnosis, histology, grade, stage, tumor size, surgery, vital status, and cause of death. Stage was categorized using Combined Summary Stage with Expanded Regional Codes (2004+). Tumor size was obtained from the Tumor Size Over Time Recode (1988+). Grade was summarized descriptively because SEER grade coding was restructured during the study period and a substantial proportion of records were coded as unknown or not applicable. Histologic terminology was interpreted within the framework of contemporary neuroendocrine neoplasm classification, which distinguishes well-differentiated NETs from poorly differentiated neuroendocrine carcinomas [20].

MP-SIR Analysis

Observed numbers of SPMs were compared with expected numbers based on population incidence rates implemented in SEER*Stat [19]. Expected counts were derived using the SEER 17 Registries excluding Alaska reference rate file (SEER 17 [excl AK] 2000–2023, Nov 2025 submission; Site recode ICD-O-3/WHO 2008), stratified by age, sex, race, calendar year, and registry. SIRs were calculated as observed divided by expected events and express the observed number of second primary malignancies relative to the number expected from age-, sex-, race-, calendar-year-, and registry-specific reference rates; they therefore represent relative incidence compared with the reference population rather than individual-level absolute risk. Ninety-five percent confidence intervals (CIs) were calculated using exact methods. Person-years at risk were accumulated according to SEER*Stat MP-SIR rules from the end of the specified latency interval until diagnosis of the selected subsequent primary malignancy, death, last follow-up, or study cutoff, as applicable.

Latency Exclusions and Sensitivity Analyses

The primary analysis excluded the first two months after the index diagnosis to reduce the contribution of synchronous detection and the initial diagnostic work-up. Previous population-based research found particularly high second-cancer incidence within the first 60 days and showed that estimates depend on the multiple-primary definition [17]. This provides an epidemiological rationale for a short primary exclusion window, but does not establish two months as an optimal cutoff or a definitive separation of synchronous and metachronous tumors. Prespecified ≥ 6 - and ≥ 12 -month analyses examined sensitivity to more conservative exclusions. The corresponding risk sets were 4,522 patients and 18,273.65 person-years at ≥ 2 months, 4,260 and 16,814.05 at ≥ 6 months, and 3,957 and 14,766.85 at ≥ 12 months.

Subgroup Analyses

Exploratory analyses considered sex, age, diagnosis

era, and stage. Site-specific and subgroup analyses were hypothesis-generating; no multiplicity adjustment was applied. Category-level observed and expected counts from SEER*Stat were summed across the component categories of each reported stratum: ages 20–39, 40–59, and ≥ 60 years; diagnosis eras 2015–2018 and 2019–2023; and regional disease by direct extension, lymph nodes, or both. The pooled SIR was the sum of observed counts divided by the sum of expected counts, with exact Poisson 95% confidence intervals for the observed total divided by the expected total. Individual category SIRs were not averaged.

Software and Ethics

Observed and expected second primary malignancy counts and the corresponding standardized incidence ratios were computed with the MP-SIR module of SEER*Stat version 9.0.43 [19]. The forest plot was generated, and the pooled subgroup standardized incidence ratios and their exact Poisson 95% confidence intervals were calculated, in Python 3.12.3 (Matplotlib 3.10.8; NumPy 2.4.4; pandas 3.0.2). This study analyzed de-identified SEER Research Plus data available to approved users under an approved SEER Research Data-use agreement [18]. The study was reviewed and approved by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University (decision no. 12, dated 30 June 2026; document reference E-60116787-020-895704). Because the SEER data are de-identified and publicly released, the requirement for individual informed consent was waived.

Results

Cohort characteristics. We identified 4,854 adults with appendiceal NET diagnosed between 2015 and 2023 (Table 1). The cohort was relatively young, with 2,367 patients (48.8%) aged 20–39 years, and predominantly female (2,995; 61.7%). Most tumors were carcinoid tumor, NOS (8240/3; 4,739; 97.6%), grade 1 (3,767; 77.6%), localized (3,517; 72.5%), and 10 mm or smaller (3,337; 68.7%); surgery of the primary site was recorded for 4,739 patients (97.6%). Over a median follow-up of 44 months (IQR, 18–74), 38 patients (0.8%) died of appendiceal NET and 132 (2.7%) died of other causes.

Overall incidence of second primary malignancy. In the primary analysis (≥ 2 -month latency exclusion; 4,522 persons, 18,273.65 person-years), 119 SPMs were observed against 103.03 expected, corresponding to an SIR of 1.15 (95% CI, 0.96–1.38). The overall incidence was therefore not significantly elevated. Estimates restricted to sites excluding non-melanoma skin cancer (SIR, 1.14; 95% CI, 0.94–1.37) and to solid tumors (SIR, 1.15; 95% CI, 0.94–1.39) were similar and likewise did not show a statistically significant excess.

Site-specific incidence. In the ≥ 2 -month latency-exclusion analysis, several site categories and subsites had 95% CIs excluding 1.0 (Table 2; Figure 1). An excess was observed for digestive system malignancies (27 observed vs 17.27 expected; SIR, 1.56; 95% CI, 1.03–2.27), with a pancreatic cancer signal among the corresponding subsites (7 observed vs 2.79 expected; SIR, 2.51; 95%

CI, 1.01–5.17). A signal was also seen for kidney and renal pelvis cancer (9 observed vs 3.81 expected; SIR, 2.36; 95% CI, 1.08–4.49); notably, the broader urinary system category was not statistically significant (11 observed vs 7.30 expected; SIR, 1.51; 95% CI, 0.75–2.70). The endocrine system showed the highest relative SIR in the primary analysis (12 observed vs 4.34 expected; SIR, 2.76; 95% CI, 1.43–4.83), largely accounted for by thyroid cancer (11 observed vs 4.02 expected; SIR, 2.73; 95% CI, 1.36–4.89). Other evaluated categories, including respiratory, breast, melanoma, male and female genital, and lymphatic and hematopoietic malignancies, did not show 95% CIs excluding 1.0 in the primary analysis.

Table 1. Baseline Characteristics of the Cohort (N = 4,854).

Characteristic	n (%)
Total	4854 (100)
Median follow-up, months (IQR)	44 (18–74)
Age 20–39	2367 (48.8)
Age 40–49	853 (17.6)
Age 50–59	782 (16.1)
Age 60–69	523 (10.8)
Age 70+	329 (6.8)
Female	2995 (61.7)
Male	1859 (38.3)
White	4067 (83.8)
Black	349 (7.2)
Asian/Pacific Islander	246 (5.1)
American Indian/AK Native	41 (0.8)
Unknown race	151 (3.1)
Dx era 2015–2018	2025 (41.7)
Dx era 2019–2023	2829 (58.3)
Carcinoid tumor, NOS (8240)	4739 (97.6)
Atypical carcinoid (8249)	112 (2.3)
EC-cell carcinoid (8241)	3 (0.1)
Grade G1	3767 (77.6)
Grade G2	268 (5.5)
Grade G3	12 (0.2)
Grade Unknown/NA	807 (16.6)
Stage Localized	3517 (72.5)
Stage Regional	1157 (23.8)
Stage Distant	62 (1.3)
Stage Unknown	118 (2.4)
Tumor size ≤ 10 mm	3337 (68.7)
Tumor size 11–20 mm	879 (18.1)
Tumor size > 20 mm	393 (8.1)
Tumor size Unknown	245 (5.0)
Surgery Yes	4739 (97.6)
Surgery No/not performed	104 (2.1)
Surgery Unknown	11 (0.2)
Cancer-specific deaths	38 (0.8)
Other-cause deaths	132 (2.7)

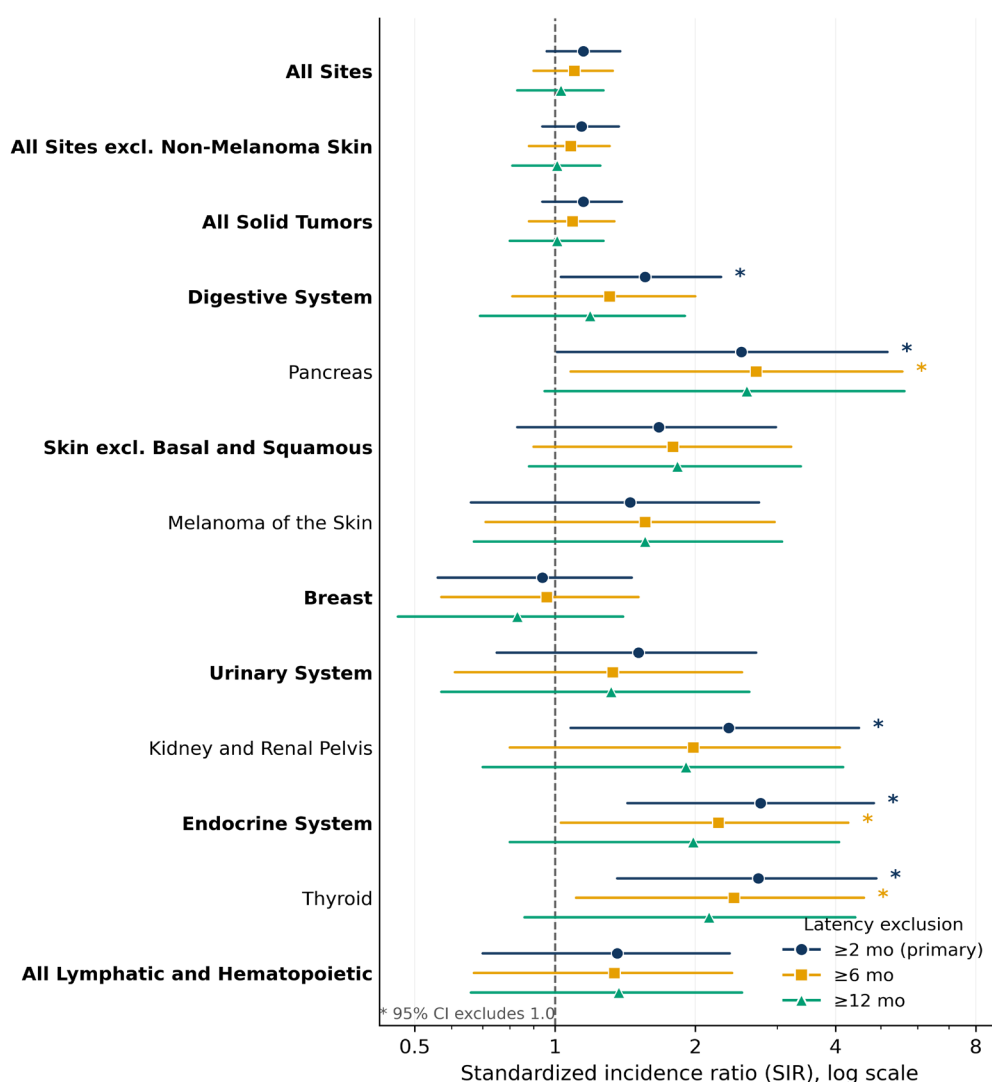


Figure 1. Standardized Incidence Ratios for Second Primary Malignancies Across Latency-Exclusion Thresholds. Selected SIRs and 95% confidence intervals on a log scale. The ≥ 2 -month analysis is primary; ≥ 6 and ≥ 12 months are sensitivity analyses. Asterisks indicate confidence intervals excluding 1.0. Kidney and renal pelvis follows the SEER recode. mo, months. Complete site-category results appear in Table 2.

Attenuation across latency. Most site-specific signals attenuated as the latency exclusion was extended, and none retained a 95% CI excluding 1.0 at the ≥ 12 -month threshold (Figure 1). For the digestive system, the SIR fell from 1.56 at ≥ 2 months to 1.31 (95% CI, 0.81–2.00) at ≥ 6 months and 1.19 (95% CI, 0.69–1.90) at ≥ 12 months. Kidney and renal pelvis followed the same pattern (2.36 $\rightarrow$ 1.98 $\rightarrow$ 1.91), as did the endocrine system (2.76 $\rightarrow$ 2.24 $\rightarrow$ 1.98) and thyroid cancer (2.73 $\rightarrow$ 2.42 $\rightarrow$ 2.14). Pancreatic cancer did not decline monotonically, remaining elevated at ≥ 6 months (SIR, 2.70; 95% CI, 1.08–5.56) before losing statistical significance at ≥ 12 months (SIR, 2.58; 95% CI, 0.95–5.62). The All Sites estimate moved toward unity across the same cutoffs (1.15 $\rightarrow$ 1.10 $\rightarrow$ 1.03), and the corresponding risk sets contracted from 4,522 to 4,260 and 3,957 persons.

Subgroup analyses. Exploratory analyses of the All Sites estimate are summarized here and in Table 3 and should be read as hypothesis-generating. By sex, the SIR was 1.23 (95% CI, 0.91–1.62) in men and 1.11 (95% CI, 0.86–1.40) in women, neither significant. By age,

point estimates were higher in younger patients (20–39 years: SIR, 1.55; 95% CI, 0.92–2.45; 40–59 years: SIR, 1.33; 95% CI, 0.99–1.75) and near unity at 60 years or older (SIR, 0.94; 95% CI, 0.70–1.24), but none reached statistical significance. Estimates were similar across diagnosis eras (2015–2018: SIR, 1.10; 95% CI, 0.87–1.37; 2019–2023: SIR, 1.27; 95% CI, 0.91–1.73). By stage, regional disease showed an elevated estimate (32 observed vs 20.52 expected; SIR, 1.56; 95% CI, 1.07–2.20), whereas localized disease (82 observed vs 79.10 expected; SIR, 1.04; 95% CI, 0.82–1.29) did not. Distant-stage disease, based on only four events, yielded an imprecise estimate whose confidence interval included unity (4 observed vs 1.61 expected; SIR, 2.49; 95% CI, 0.68–6.37). Although the regional-stage subgroup included 1,157 patients at baseline, its estimate rested on 32 observed versus 20.52 expected events and arose among multiple exploratory comparisons; it should therefore be regarded as hypothesis-generating. The baseline subgroup size is distinct from the number entering the latency-eligible analysis.

Table 2. Standardized Incidence Ratios for Second Primary Malignancies, by Latency Exclusion

Site / cancer type	O (≥ 2 mo)	E (≥ 2 mo)	SIR (95% CI) ≥ 2 mo	SIR (95% CI) ≥ 6 mo	SIR (95% CI) ≥ 12 mo
All Sites	119	103.03	1.15 (0.96–1.38)	1.10 (0.90–1.33)	1.03 (0.83–1.27)
All Sites excl. Non-Melanoma Skin	117	102.65	1.14 (0.94–1.37)	1.08 (0.88–1.31)	1.01 (0.81–1.25)
All Solid Tumors	104	90.74	1.15 (0.94–1.39)	1.09 (0.88–1.34)	1.01 (0.80–1.27)
Oral Cavity and Pharynx	1	2.58	0.39 (0.01–2.16)	0.42 (0.01–2.32)	0.47 (0.01–2.61)
Digestive System	27	17.27	1.56* (1.03–2.27)	1.31 (0.81–2.00)	1.19 (0.69–1.90)
Pancreas	7	2.79	2.51* (1.01–5.17)	2.70* (1.08–5.56)	2.58 (0.95–5.62)
Respiratory System	5	10.50	0.48 (0.15–1.11)	0.51 (0.17–1.20)	0.57 (0.19–1.34)
Bones and Joints	0	0.19	0.00 (0.00–19.81)	0.00 (0.00–21.46)	0.00 (0.00–24.31)
Soft Tissue incl. Heart	0	0.73	0.00 (0.00–5.04)	0.00 (0.00–5.44)	0.00 (0.00–6.13)
Skin excl. Basal and Squamous	11	6.61	1.67 (0.83–2.98)	1.79 (0.90–3.21)	1.83 (0.88–3.37)
Melanoma of the Skin	9	6.23	1.45 (0.66–2.74)	1.56 (0.71–2.96)	1.56 (0.67–3.07)
Breast	19	20.28	0.94 (0.56–1.46)	0.96 (0.57–1.51)	0.83 (0.46–1.40)
Female Genital System	6	8.07	0.74 (0.27–1.62)	0.80 (0.29–1.74)	0.75 (0.24–1.75)
Male Genital System	12	11.57	1.04 (0.54–1.81)	1.12 (0.58–1.95)	0.94 (0.43–1.78)
Urinary System	11	7.30	1.51 (0.75–2.70)	1.33 (0.61–2.52)	1.32 (0.57–2.61)
Kidney and Renal Pelvis	9	3.81	2.36* (1.08–4.49)	1.98 (0.80–4.08)	1.91 (0.70–4.15)
Brain and Other Nervous System	1	1.30	0.77 (0.02–4.29)	0.83 (0.02–4.63)	0.94 (0.02–5.22)
Endocrine System	12	4.34	2.76* (1.43–4.83)	2.24* (1.03–4.26)	1.98 (0.80–4.07)
Thyroid	11	4.02	2.73* (1.36–4.89)	2.42* (1.11–4.60)	2.14 (0.86–4.41)
All Lymphatic and Hematopoietic	12	8.84	1.36 (0.70–2.37)	1.34 (0.67–2.40)	1.37 (0.66–2.52)

O, observed events; E, expected events; SIR, standardized incidence ratio; CI, confidence interval; mo, months; excl., excluding; incl., including. O and E refer to the ≥ 2 -month analysis only. The ≥ 6 - and ≥ 12 -month thresholds are sensitivity analyses. Persons at risk / person-years: ≥ 2 mo, 4,522 / 18,273.65; ≥ 6 mo, 4,260 / 16,814.05; ≥ 12 mo, 3,957 / 14,766.85. *95% CI excludes 1.0. Organ subsites overlap their parent categories and must not be summed with them.

Table 3. Exploratory Subgroup Standardized Incidence Ratios

Subgroup	SPM outcome	SIR (95% CI)
Men	All sites	1.23 (0.91–1.62)
Women	All sites	1.11 (0.86–1.40)
Age 20–39 years	All sites	1.55 (0.92–2.45)
Age 40–59 years	All sites	1.33 (0.99–1.75)
Age ≥ 60 years	All sites	0.94 (0.70–1.24)
Diagnosis 2015–2018	All sites	1.10 (0.87–1.37)
Diagnosis 2019–2023	All sites	1.27 (0.91–1.73)
Localized stage	All sites	1.04 (0.82–1.29)
Regional stage	All sites	1.56 (1.07–2.20)
Distant stage	All sites	2.49 (0.68–6.37)
Women	Pancreas	3.82 (1.40–8.30)
Women	Thyroid	2.71 (1.24–5.14)

Primary ≥ 2 -month latency exclusion. SPM, second primary malignancy; SIR, standardized incidence ratio; CI, confidence interval. All estimates are exploratory and unadjusted for multiple comparisons. Observed/expected events: localized stage, 82/79.10; regional stage, 32/20.52; distant stage, 4/1.61. The regional baseline subgroup contains 1,157 patients; this is not the latency-eligible analysis count. Subgroup denominators and person-years are not presented here and should not be inferred from baseline counts. Women-specific organ estimates overlap the all-site estimates.

Discussion

In this contemporary cohort of adults with appendiceal NETs, the overall incidence of second primary malignancies

was not significantly higher than expected from reference population rates. The primary analysis included 119 observed versus 103.03 expected events (SIR, 1.15; 95% CI, 0.96–1.38). The overall SIR approached unity with longer latency exclusions. Several organ-specific estimates were elevated initially, but none had a confidence interval excluding unity at ≥ 12 months. This loss of statistical significance does not establish the absence of an excess, particularly for sites with few events and wide confidence intervals.

Previous SEER research identified an increased incidence of second cancers across NET populations, with variation by primary site [11]. An English registry study described additional site-specific associations [12], while a separate SEER analysis examined the association between second primaries and survival [13]. Studies of colorectal, rectal, and pancreatic neuroendocrine neoplasms provide further context [14–16]. These populations differ from appendiceal NETs in age, histology, stage, and competing mortality. Our focus on appendiceal NETs diagnosed during 2015–2023, together with repeated latency exclusions, addresses whether findings from broader NET populations persist in this specific contemporary cohort.

The timing of detection is important because multiple-primary definitions and exclusion of early events can affect incidence estimates [17]. Digestive, pancreatic, and renal malignancies may be detected during investigations surrounding an appendiceal diagnosis. Thyroid cancer is also susceptible to incidental detection and overdiagnosis [21, 22]. These are possible

explanations, supported by general work on detection and surveillance bias [23, 24], rather than mechanisms demonstrated by our data. SEER does not record the imaging, endoscopy, or surveillance intensity needed to test them directly.

The latency analyses require a distinction between changes in point estimates and changes in precision. Digestive, kidney and renal pelvis, and thyroid SIRs decreased as the exclusion interval lengthened. Pancreatic SIRs, however, remained similar (2.51, 2.70, and 2.58 at ≥ 2 , ≥ 6 , and ≥ 12 months). The ≥ 12 -month pancreatic confidence interval included unity but remained wide (0.95–5.62). Longer exclusions also reduced person-time and the population at risk. Consequently, attenuation of some estimates and loss of statistical significance cannot alone establish surveillance bias or exclude a persistent site-specific excess.

The subgroup findings are exploratory

The regional-stage subgroup included 1,157 patients at baseline, whereas its SIR was based on 32 observed versus 20.52 expected events. These baseline patients should not be equated with the latency-eligible analysis population. The estimate arose among multiple comparisons and may reflect residual confounding or differences in diagnostic intensity. Regional and nodal classifications in appendiceal NETs also require careful interpretation [25]. The female-specific pancreatic and thyroid estimates in Table 3 similarly warrant caution because of their wide confidence intervals. Statistical significance in one subgroup and its absence in another do not establish a difference between subgroups.

Clinical follow-up should remain consistent with established appendiceal NET guidance, including the ENETS recommendations [8, 9]. Our results do not provide evidence to introduce additional routine organ-directed screening solely because of a previous appendiceal NET. Age-appropriate population screening and evaluation of symptoms or incidental findings remain appropriate. This interpretation does not replace NET-specific follow-up for patients with adverse tumor features, nor screening indicated by hereditary predisposition or other individual risk factors [8–10].

Strengths include the population-based cohort, defined appendiceal histologies, and sensitivity analyses using longer exclusion intervals. Limitations include the absence of individual surveillance, hereditary, lifestyle, and detailed treatment data; possible misclassification; and limited follow-up for an indolent disease. The 2018 change in SEER grade coding may have reduced comparability across diagnosis years and contributed to unknown or not-applicable records. Grade was descriptive and did not define the cohort or primary analysis. Multiple unadjusted comparisons and small organ-specific event counts limit inference. SIRs describe relative incidence against population rates, not individual absolute risk or causation. The findings may not generalize beyond the populations covered by the selected registries.

In conclusion, this cohort did not show a statistically significant overall excess of second primary malignancies. Several early site-specific estimates were elevated; some

declined with longer exclusions, whereas the pancreatic estimate remained elevated but imprecise. No site-specific confidence interval excluded unity at ≥ 12 months. These findings do not support routine additional organ-directed screening based solely on appendiceal NET history, but longer follow-up and more detailed data are needed to assess possible late excess incidence.

Author Contribution Statement

T.D. conceived and designed the study, acquired and analyzed the SEER data, interpreted the results, and drafted and revised the manuscript. T.G.K. contributed to data interpretation, critically revised the manuscript for important intellectual content, and approved the final version. Both authors read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Ethical approval

This study analyzed de-identified, publicly available SEER Research Plus data under an approved data-use agreement and was approved by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University (decision no. 12, dated 30 June 2026; E-60116787-020-895704). Individual informed consent was waived. The study was not conducted as part of a student thesis.

Data availability

SEER data are available at <https://seer.cancer.gov> following approval of a SEER Research Data-use agreement; the authors cannot redistribute individual-level data. Derived summary outputs are available from the corresponding author on reasonable request.

Registration

Not applicable. This observational, registry-based study is not a clinical trial, systematic review, or meta-analysis and was not registered in a registration dataset.

Conflict of interest

The authors declare no conflicts of interest.

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