

# The crucial role of age and site in incidence and prognosis of female neuroendocrine neoplasms in the United States: a population-based study from 2000 to 2018

Guixiu Xiao<sup>1,2</sup>, Zihan Xu<sup>3,\*</sup>, Yong Zhang<sup>1,2,\*</sup>, Shuang Dai<sup>1,2</sup>, Ganlu Ouyang<sup>1,2</sup>, Yan Huang<sup>1,2</sup>, Yanyang Liu<sup>1,2</sup>, Dan Cao<sup>4</sup>, Feng Luo<sup>1,2</sup>

<sup>1</sup>Department of Medical Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

<sup>2</sup>Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China

<sup>3</sup>Laboratory of Integrative Medicine, Clinical Research Center for Breast, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University and Collaborative Innovation Center, Chengdu, Sichuan, China

<sup>4</sup>Abdominal Oncology Ward, Division of Medical Oncology, Cancer Center, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, Sichuan, China

\*Equal contribution and shared first authorship

**Correspondence to:** Dan Cao, Feng Luo; **email:** [caodan@scu.edu.cn](mailto:caodan@scu.edu.cn); [huaxiluofeng@sina.com](mailto:huaxiluofeng@sina.com), <https://orcid.org/0000-0003-4008-271X>

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## ABSTRACT

**Background:** As the incidence continues to rise, global concern about neuroendocrine neoplasms (NENs) is mounting. However, little is known about how NENs affect women patients.

**Methods:** The annual percentage change (APC) was calculated to describe the incidence. Cox proportional hazards multivariable regression was used to identify risk factors. The nomograms were employed to estimate prognosis.

**Results:** A total of 39,237 female NENs (fNENs) cases were identified. The incidence of fNENs increased annually (APC = 4.5, 95% CI 4.1-4.8,  $P < 0.05$ ), and the incidence pattern and survival outcomes showed age and site-specificity. Appendiceal, rectal, and pulmonary fNENs were major contributors to the incidence of patients younger than 40, between 40-59, and over 60 years old, respectively. The Cox proportional hazards regression model revealed that age, tumor size, grade, stage, and primary sites were closely related to survival. The worst survival outcomes appeared in breast, reproductive system, and liver fNENs for patients under 40, between 40-49, and over 50 years old, respectively. A nomogram based on these developed with higher predictive accuracy of prognosis, with a C index of 0.906 in the training cohort and 0.901 in the validation cohort.

**Conclusions:** Our findings revealed distinct site-specific tendencies in the incidence and survival patterns among fNEN patients across various age groups. Thus, reasonable patient screening and stratification strategies should be implemented, especially for young patients.

## INTRODUCTION

Neuroendocrine neoplasms (NENs) are rare cancers derived from neuroendocrine cells that share features of neural and endocrine differentiation [1]. NENs consist of

a heterogeneous group of neoplasms that can occur in almost all sites, most frequently in the digestive and respiratory system [2, 3]. The steady increase of NENs over the past decades has received global attention, accordingly, tremendous efforts have been made in

superior classification, molecular diagnosis, radionuclide, and targeted therapies of NENs [3–7]. However, the epidemiological characteristics and prognostic factors, crucial for early perception and risk stratification, have not been fully understood, particularly for women patients.

Gender heterogeneity exists in the incidence, prevalence, and outcomes of various types of cancer, including NENs [8–11]. For instance, the increased incidence of women patients was almost twice as much as men in lung atypical carcinoid and typical carcinoid [12]. Another study showed that the incidences between genders were almost similar previously, but the incidence in females has increased at a more rapid rate than in males since 2013 [13]. Understanding these differences can aid the development of more effective prevention and treatment strategies for both male and female patients. Unfortunately, previous studies had enrolled both men and women, but only as a covariate instead of conducting specifically gender-specific analysis [14–16]. Therefore, there is a critical need to investigate the epidemiological characteristics of female NENs (fNENs) for more accurate clinical recognition and treatment.

Here, we performed a population-based study using the data from the Surveillance, Epidemiology, and End Results (SEER) database to analyze the clinicopathologic features and prognostic characteristics of fNENs. Our goal was to provide a comprehensive description of demographic characteristics and recent incidence trends of fNENs and establish a nomogram model for prognostic assessment to assist clinical decision-making.

## MATERIALS AND METHODS

### Data source

The SEER database, a national cancer registry, is an authoritative source of information on cancer epidemiology and clinical characteristics in the United States. In this retrospective cohort study of fNENs from 2000 to 2018, we used the data from the SEER database (SEER-17). Patients of fNENs were identified based on the histologic codes from the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) (Supplementary Table 1). The inclusion and exclusion criteria are shown in Supplementary Figure 1. Patient characteristics, including age, race, primary site, size of the primary tumor, stage, grade, year of diagnosis, marital status, and survival were obtained from the SEER database. The West China Hospital of Sichuan University institutional review board deemed this study exempt from review and informed consent because the data are freely available.

### Classification of variables

The population was divided into 2 groups by 50 years old firstly because we found a great gap in people younger or older than 50 years old. 10 years were used as a period for detailed analysis and participants younger than 30 or over 80 years old are grouped separately because they are less numerous. We assigned race/ethnicity as Hispanic, non-Hispanic white (NHW), non-Hispanic black (NHB), non-Hispanic Asian or Pacific Islander (NHAPI), and non-Hispanic American Indian/Alaska Native (NHAIAN). The stage was categorized as localized, regional, or distant according to the SEER staging system. The grade was divided into 4 groups: grade (G) 1, well-differentiated; G 2, moderately differentiated; G3, poorly differentiated; G 4, undifferentiated or anaplastic. For the site of the primary tumor, we analyzed breast, female reproductive system (including the uterus, ovary, vulva, and vagina), and other common organs of NENs (appendix, rectum, small intestine, pancreas, lung, stomach, colon, and cecum). Due to the median overall survival (OS) not reaching in some groups, we use 3-year and 5-year survival rates to evaluate the survival as supplementary.

### Nomogram construction and validation

Nomograms, which generate an individual numerical probability of events by integrating diverse prognostic and determinant variables, were used to estimate prognosis [17]. All eligible patients ( $n = 13,496$ ) were divided into 2:1 training ( $n = 9,010$ ) and validating ( $n = 4,505$ ) groups by simple randomization. The factors of interest associated with OS from Multivariable Cox proportional hazards regression models were used to establish the prediction model. The verification of the nomogram is based mainly on the internal (training cohort) and external (validation cohort) discrimination and calibration measurements. The consistency index (C index) was used to evaluate the discriminative ability of the nomogram and the calibration curve was used to compare predicted survival according to the nomogram and actual survival.

### Statistical analysis

Statistical analysis was conducted from December 2022 to March 2023. Descriptive statistics t-tests or  $\chi^2$  tests were used to compare patients' basic clinical characteristics.

The age-adjusted incidence was calculated by the SEER\*Stat software, version 8.4.0.1. Yearly incidence per 100,000 persons was age-adjusted to the 2000 US standard population. The annual percentage change (APC) was calculated by fitting a simple linear model.

Cox proportional hazards multivariable regression was used to evaluate the association of age, race/ethnicity, Marital status, tumor size, stage, grade, and site with OS by calculating hazard ratios (HRs) and 95% CIs with other factors adjusted. Statistical analyses were conducted with SPSS, version 23 (IBM Corp). All *P*-values were from 2-sided tests, and results were deemed statistically significant at *P* < 0.05.

## RESULTS

### Demographic and clinicopathological characteristics

A total of 39,237 fNEN cases were identified during the study period from the SEER-17 database (Table 1). More patients were diagnosed with fNENs over 50 years old (n=30,108, 76.7%). Among all patients, 63.7% (n=25,010) were white, 14.5% (n=5,682) were black, 13.5% (n=5,293) were Hispanic, and the majority of patients had tumors less than 20 millimeters (n=15,742, 40.1%). In addition, 32.2% (n=12,640) were in G1, 8.1% (n=3,172) were in G2, 7.3% (n=2,845) were in G3, 2.5% (n=979) were in G4, and 50.0% (n=19,601) were unknown. As for the stage, more patients had localized stage (n=16,736, 42.7%), while others had regional (n=5,952, 15.2%) and distant stage (n=7,606, 19.4%). The most common sites of primary cancer were lung (n=9,415, 24.0%), followed by rectum (n=6,958, 17.7%), small intestine (n=5,977, 15.2%), pancreas (n=3,637, 9.3%), appendix (n=3,136, 8.0%), stomach (n=2,746, 7.0%), colon (n=1,244, 3.2%), female reproductive system (n=922, 2.3%), cecum (n=889, 2.3%) and breast (n=252, 0.6%).

### Annual incidence

We used population data from the SEER program to calculate the age-adjusted incidence of fNENs per 100,000 individuals per year with a population of 2000 as the standard population. The age-adjusted incidence of fNENs increased from 3.2 to 6.3 per 100,000 from 2000 to 2018, with an APC of 4.5 (95%CI, 4.1-4.8) (Figure 1A). The increasing incidence of fNENs was found in all age groups, while the majority of fNENs patients (76.7%) were over 50 years old (Figure 1B). This upward trend was also observed in almost all race, grade, and stage groups, with the most noticeable increase in Hispanic (APC, 5.4; 95%CI, 4.7-6.1), Grade 1 (APC, 19.4; 95%CI, 17.6-21.3) and localized fNENs (APC, 6.6; 95%CI, 6.0-7.2) (Figure 1C–1E). With regard to the primary sites, fNENs diagnosed at lung, appendix, rectum, small intestine, pancreas, and stomach increased over time. The most remarkable increases were reported in appendix (APC, 19.3; 95%CI, 16.0-22.7), followed by pancreas (APC, 8.6; 95%CI, 7.7-9.6), stomach (APC, 6.3; 95%CI, 5.4-7.2),

small intestine (APC, 4.5; 95%CI, 3.9-5), rectum (APC, 3.7; 95%CI, 2.9-4.5), and lung (APC, 1.8; 95%CI, 1.2-2.4) (Figure 1F).

### Incidence according to site and age

Due to the significant disparities of different ages and tumor sites, we programmed an in-depth analysis of the incidence of fNENs patients (Figure 2 and Supplementary Figure 2). The increasing incidence of fNENs was found in almost all age groups (Supplementary Figure 2A). In young fNENs (<40 years old), the overall incidence was low while appendiceal fNENs showed significant growth in the last 10 years (Figure 2A, 2B and Supplementary Figure 2F). Rectum fNENs played a dominant role in patients aged 40-59 years old, and pulmonary fNENs in patients over 60 years old (Figure 2C–2G).

For the age distribution of fNENs patients with common sites, the major population was over 50 years old in pulmonary, pancreatic, and small intestinal fNENs (Supplementary Figure 2B–2D), and 50-59 years old seemed to be the period of high incidence of rectal fNENs (Supplementary Figure 2E). Although there were similar increasing trends in all age groups in appendiceal fNENs, the number of young patients was a little bit more (Supplementary Figure 2F).

In terms of overall absolute number and percentage, the lung was the most frequent site of fNENs and was inclined to occur after 50 years old (Figure 3A). Similarly, the number of fNENs located in the stomach, small intestine, rectum, and pancreas had an abrupt growth after 50 years old (Figure 3A). The proportion of fNENs in different sites for each age group is presented in Figure 3B. The results also showed that fNENs of the appendix and female reproductive system have a higher proportion in young patients versus the elderly. Whereas the incidence of pulmonary and intestinal fNENs was markedly higher among older than younger women.

### Survival

The median OS of all fNENs patients was 15.0 years (180.1 months) and 5-year survival was 80.5% (Figure 4). The overall prognosis of young patients was better than that of the elderly and rectal fNENs had the best survival in all site groups (Figure 4). In patients under 50 years old, only pancreatic fNENs reached median OS (17.7 years) and fNENs of the breast had the worst 5-year survival rate (57.6%) (Table 2). While in those older than 50 years old, the worst 5-year survival rate was found in hepatic fNENs. Patients diagnosed with G1 (17.7 years) or G2 (14.4 years) had a significantly

**Table 1. Demographic and clinicopathological characteristics of female neuroendocrine neoplasms (fNENs) patients from 2000 to 2018.**

<b>Variables</b>	<b>N</b>	<b>%</b>
<b>Enrolled patients</b>	39237	100.0
<b>Age at initial diagnosis, years</b>		
< 50	9129	23.3
≥ 50	30108	76.7
<b>Race</b>		
Hispanic	5293	13.5
NHW	25010	63.7
NHB	5682	14.5
NHAIAN	259	0.7
NHAPI	2323	5.9
Unknow	670	1.7
<b>The year of diagnosis</b>		
2000-2004	6523	16.6
2005-2009	8699	22.2
2010-2014	11566	29.5
2015-2018	12449	31.7
<b>Marital status</b>		
Single	6912	17.6
Married	18609	47.4
Divorced/widowed/separated	10154	25.9
Unknown	3562	9.1
<b>Tumor Size (mm)</b>		
≤ 20	15742	40.1
21-40	6327	16.1
≥ 41	4626	11.8
Unknown	12542	32.0
<b>GRADE</b>		
1	12640	32.2
2	3172	8.1
3	2845	7.3
4	979	2.5
Unknown	19601	50.0
<b>Disease stage</b>		
Localized	16736	42.7
Regional	5952	15.2
Distant	7606	19.4
Unstaged	8943	22.8
<b>Primary tumor sites</b>		
Appendix	3136	8.0
Rectum	6958	17.7
Small intestine	5977	15.2
Pancreas	3637	9.3
Lung	9415	24.0
Stomach	2746	7.0
Colon	1244	3.2
Reproductive system	922	2.3
Cecum	889	2.3
Breast	252	0.6

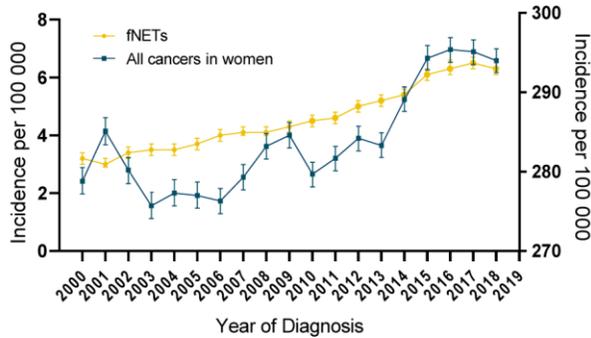
NHW indicates Non-Hispanic White; NHB, Non-Hispanic Black; NHAIAN, Non-Hispanic American Indian/Alaska Native; NHAPI, Non-Hispanic Asian or Pacific Islander; mm, millimeter; Grade 1, Well differentiated; Grade 2, Moderately differentiated; Grade 3, Poorly differentiated; Grade 4, Undifferentiated, anaplastic.

better median OS than G3 (5.2 years) or G4 (4.7 years) (Figure 4 and Supplementary Figure 3A). For the different stages, the median OS was 18.6 years in localized, 14.4 years in regional, and 6.8 years in distant stages (Figure 4 and Supplementary Figure 3B). There seemed to be no obvious difference in the survival between different races (Figure 4 and Supplementary Figure 3C). The fNENs in rectum (17.8 years), stomach (16.3 years), appendix (15.6 years), and small intestine

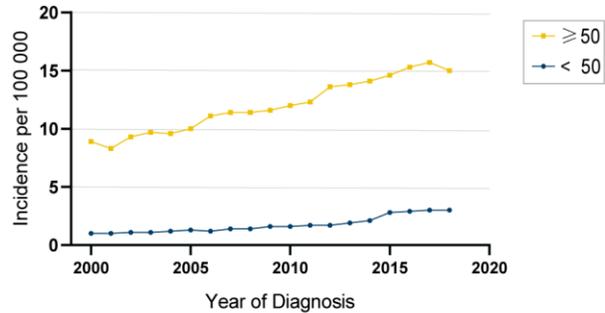
(15.4 years) had better prognosis among site groups, while fNENs in liver (6.6 years) and female reproductive system (8.8 years) had worse outcomes (Figure 4 and Supplementary Figure 3D).

Then, we further analyzed the survival outcomes according to age and site (Supplementary Table 2). When age was divided more detailed, rectal fNENs still had the highest survival rate in almost all age groups. The

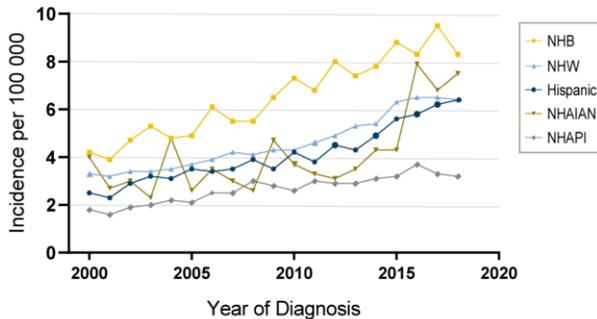
**A** Annual incidence of fNENs and all cancers



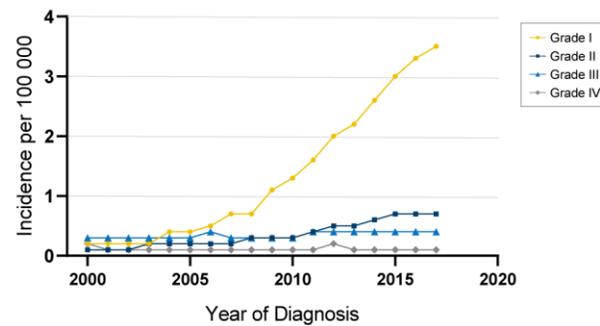
**B** Annual incidence of fNENs by age



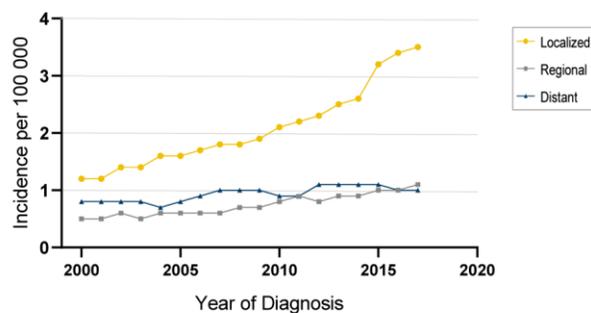
**C** Annual incidence of fNENs by race



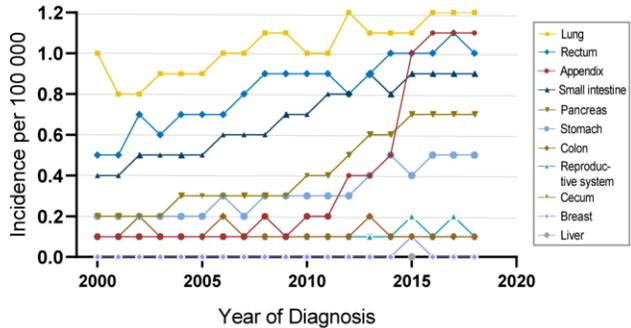
**D** Annual incidence of fNENs by grade



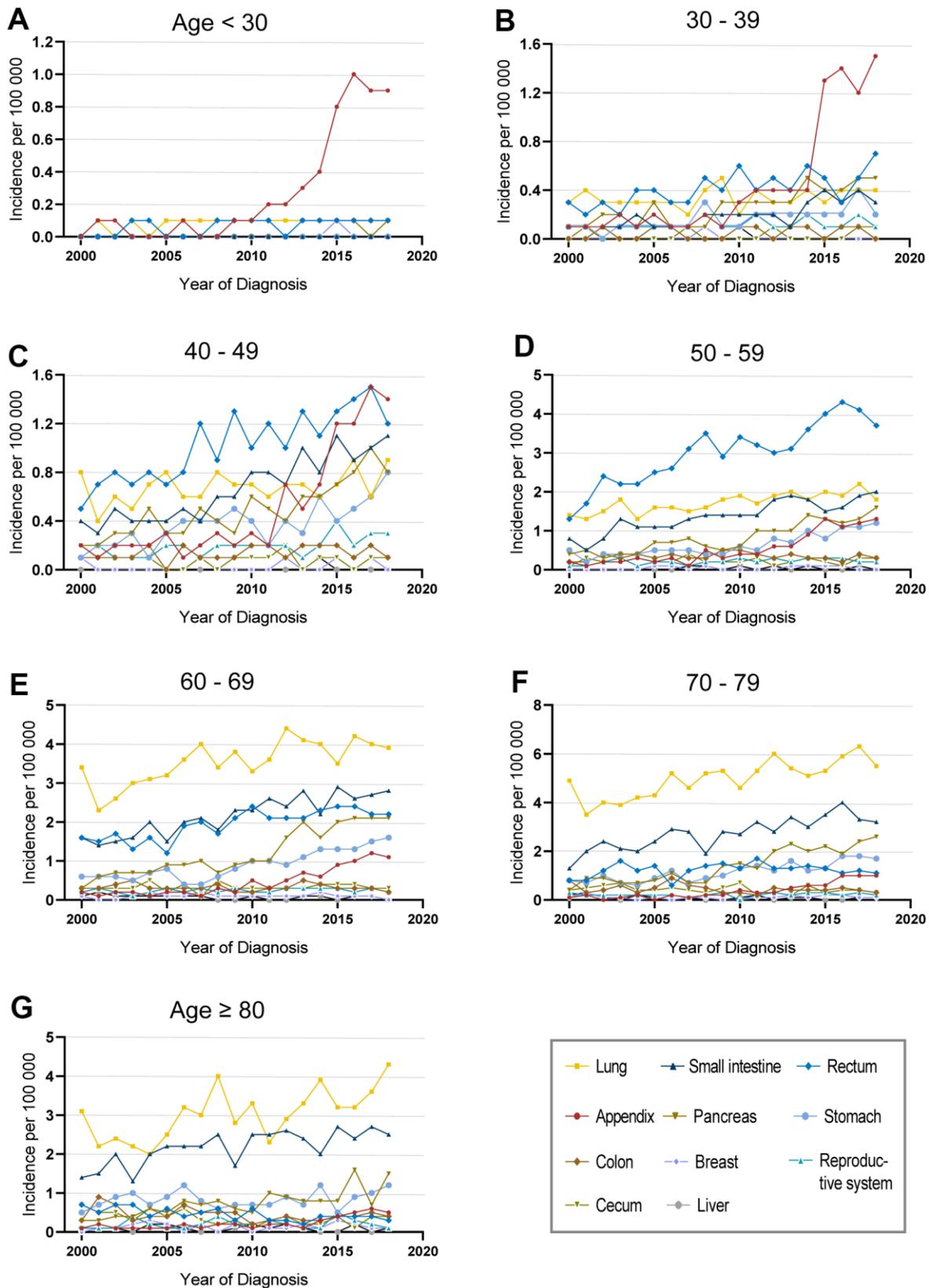
**E** Annual incidence of fNENs by stage



**F** Annual incidence of fNENs by site



**Figure 1. Morbidity tendency of female neuroendocrine neoplasms (fNENs) patients by age, race, stage, grade, and site.** (A) The age-adjusted incidence of women patients in all cancers (right Y) and Neuroendocrine neoplasms (NENs) (left Y) during 2000-2018. (B) The fNENs incidence by age. (C) The incidence of fNENs in different races. (D) The incidence of fNENs by grade. (E) Incidence of fNENs by stage. (F) The incidence of fNENs by the site.



**Figure 2. Incidence of female neuroendocrine neoplasms (fNENs) patients with different sites in various age groups.** The incidence of fNENs by site in patients younger than 30 years old (A), between 30-39 years old (B), between 40-49 years old (C), between 50-59 years old (D), between 60-69 years old (E), between 70-79 years old (F) and over 80 years old (G).

survival of pulmonary fNENs showed a continued and obvious decline after 40 years old. However, the breast fNENs seemed to have the worst survival in young patients (age<40). In addition, the worst survival rate was shown in fNENs of the reproductive system aged 40-49 years old and fNENs of liver in those over 50 years old.

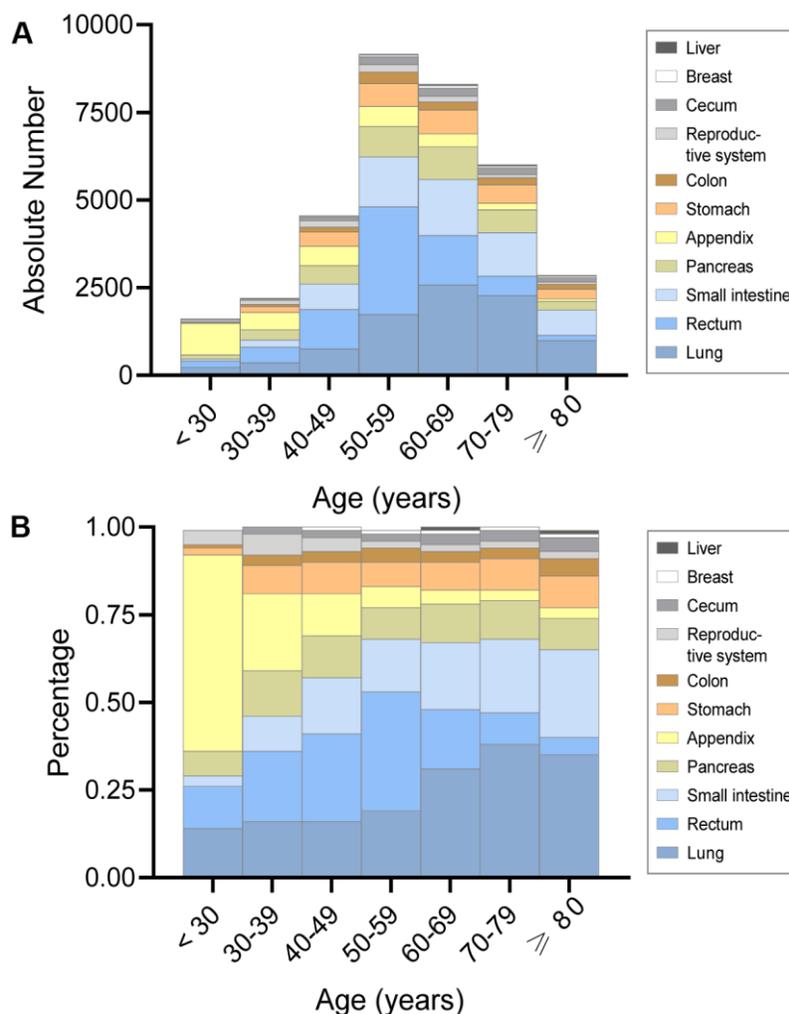
### Multivariable analysis

To identify the independent prognostic risk factors, we performed a multivariable analysis. The Cox proportional hazards regression model revealed that age, tumor size, grade, stage, and primary site were closely related to survival (Figure 4). Compared with the patients younger than 50 years old, the risk of death for the older was increased (HR, 1.58; 95%CI, 1.41-1.77). The prognosis was poorer for fNENs with G3 (HR, 7.14; 95%CI, 6.36-8.02) and G4 (HR, 7.14;

95%CI, 6.18-8.24) than for those with G1 and G2 (HR, 2.091; 95%CI, 1.85-2.37) after adjustment for other covariates. Overall survival was worse for patients with distant NENs (HR, 9.21; 95%CI, 8.00-10.60) than localized NENs. When we used appendiceal NENs as a reference, we observed that fNENs of other sites all had a higher risk of death. Among them, fNENs of small intestine (HR, 2.15, 95%CI, 1.70-2.72), pancreas (HR, 2.41; 95%CI, 1.93-3.01), lung (HR, 2.13, 95%CI, 1.59-2.85), stomach (HR, 2.63, 95%CI, 2.03-3.41), and colon (HR, 2.65; 95%CI, 2.04-3.43) had higher risk of death than appendiceal NENs, in which liver fNENs was the most dangerous (HR, 6.17; 95%CI, 4.27-8.89).

### Nomograms

A collection of 13,496 eligible patients from previous cohorts was included in the study according to the



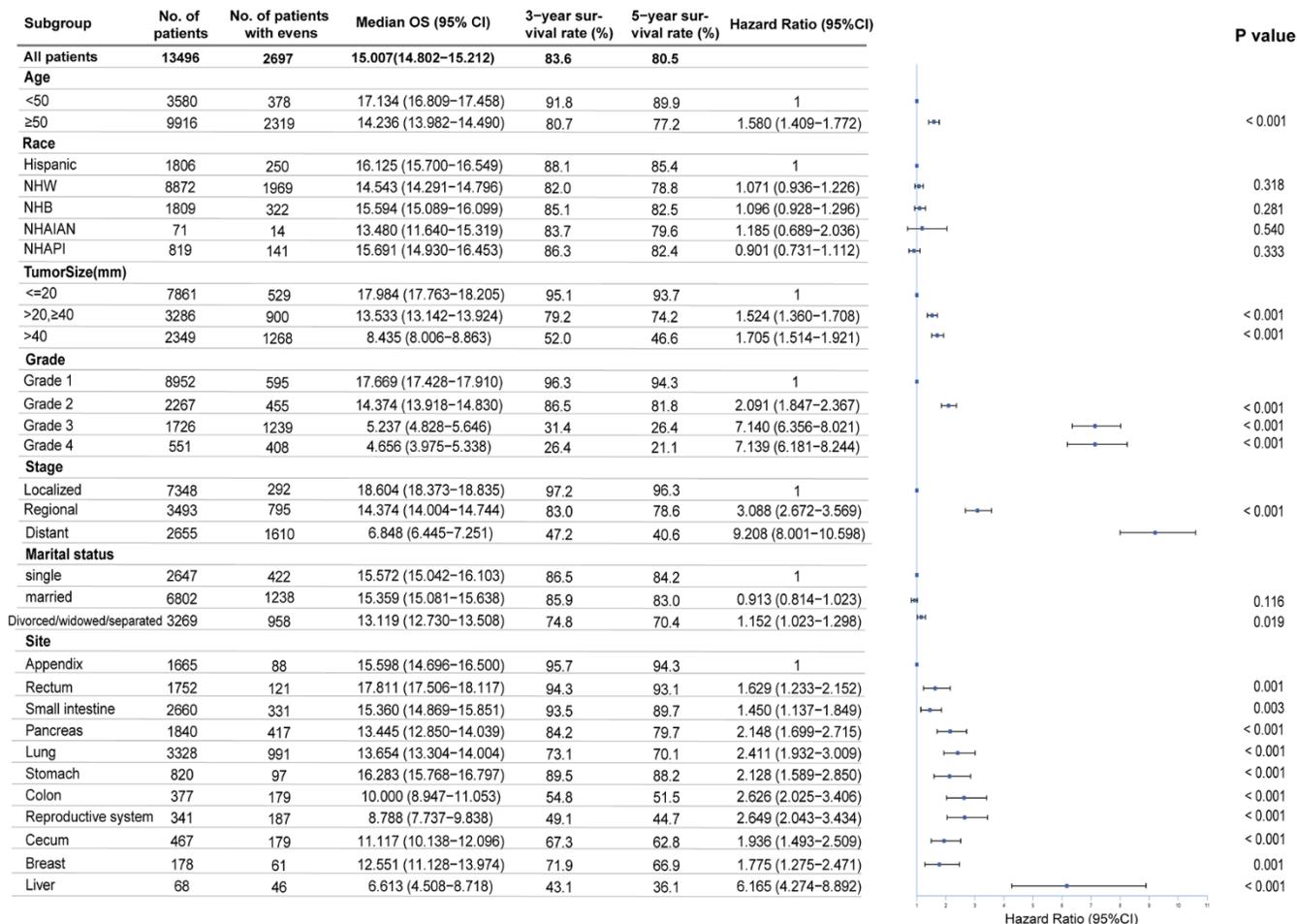
**Figure 3. The absolute number and proportion of incidence in female neuroendocrine neoplasms (fNENs) by site for each age group. (A) The number of fNENs patients with various sites in each age group. (B) The proportion of fNENs patients with various sites in each age group.**

model-building requirements (Supplementary Figure 1). Then they were randomly divided into a training set and a validation set by a ratio of 2:1. The training and validation cohorts were comparable in terms of demographic and clinical characteristics ( $P > 0.05$ ) (Supplementary Table 3). According to the results of the Cox proportional hazards regression model, the prediction model contains age, tumor size, grade, stage, and primary site. Consistent with the previous analysis results, the disease stage had the greatest significance, contributing a maximum of 100 points. Grade (91 points), primary tumor site (89 points), age (85 points), and tumor size (26 points) were also individually associated with OS (Figure 5A). Then we internally and externally validated the nomogram, the C indexes for OS prediction of the training cohort (internal validation) and validation cohort (external validation) in the nomogram were 0.906 (95% CI, 0.900-0.912) and 0.901 (95% CI, 0.902-0.918), respectively. Finally, the

calibration plots of the nomogram showed consistency between the nomogram-predicted and actual outcomes in the internal (Figure 5B) and external (Figure 5C) validation.

## DISCUSSION

Previous studies have reported the increased incidence of NENs worldwide, in which approximately 50% were female patients [14, 15]. Gender differences in the incidence, diagnosis, and prognosis of NENs have been reported, while there is still a lack of overall epidemiological description and prognostic risk assessment for fNENs patients [14, 18, 19]. Our analysis for fNENs discovered that fNENs of appendix, rectum, and lung had the highest incidence in the young (<40), middle-aged (40-59), and elderly ( $\geq 60$ ), respectively. Additionally, fNENs of the breast, reproductive system, and liver had the worst survival in



**Figure 4. Multivariable regression analysis for female neuroendocrine neoplasms (fNENs).** OS, overall survival; NHW, Non-Hispanic White; NHB, Non-Hispanic Black; NHAIAN, Non-Hispanic American Indian/Alaska Native; NHAPI, Non-Hispanic Asian or Pacific Islander; mm, millimeter; Grade 1, Well differentiated; Grade 2, Moderately differentiated; Grade 3, Poorly differentiated; Grade 4, Undifferentiated, anaplastic.

**Table 2. Survival analysis of female neuroendocrine neoplasms (fNENs) patients: actuarial survival of fNENs patients diagnosed from 2000 to 2018 by age and primary tumor site.**

Tumor site	Age <50			Age ≥50		
	Median survival (Years)	Survival rate (%)		Median survival (Years)	Survival rate (%)	
		3-Year	5-Year		3-Year	5-Year
All	NR	88.7	86.1	NR	72.3	68.7
best	NR	97.7	97.4	NR	96.7	95.9
Appendix	NR	97.6	95.7	NR	86.9	82.6
Stomach	NR	94.7	95.0	NR	90.0	89.2
Small intestine	NR	97.1	95.0	NR	90.0	85.0
Lung	NR	86.9	85.4	18.5	60.3	57.1
Colon	NR	80.0	76.1	19.5	63.8	61.2
Cecum	NR	79.4	76.7	15.3	67.8	62.6
Pancreas	17.7	80.1	73.5	8.8	66.6	59.6
Breast	NR	62.1	57.6	15.0	68.5	62.9
Reproductive system	NR	65.0	62.1	2.7	49	44.7
Liver	NR	74.8	71.7	1.5	39.8	31.4

patients younger than 50, between 50 to 59, and those older than 60 years old, respectively. At the same time, the predictive models incorporating detailed age and site also showed superior predictive power. Our results demonstrated that gender differences are also worthy of attention in fNEN. The distinct tendency in various age groups with different tumor sites confirmed the importance and necessity of implementing early screening, patient stratification, and precision medicine for specific populations with different ages and sites.

Consistent with previous reports, the age-adjusted annual incidence of fNENs has gradually risen over the past decade, in which Grade 1 and localized fNENs rose markedly [14, 15]. This is possibly attributed to the detection of asymptomatic early-stage disease after the extensive use of endoscopy and computed tomography [20]. Notably, the morbidity of different sites presented obvious discriminations. Developments in imaging examinations make fNENs at lung, rectum, small intestine, pancreas, and stomach easier to be diagnosed and therefore benefit a lot. Although fNENs of the lung, rectum and intestine occupy the majority, the appendiceal fNENs showed an unexpectedly tremendous increase (11-fold). Interestingly, the phenomenon was observed in recent years, partly attributed to a better understanding of the pathophysiologic presentation of NENs, improved classification system, as well as availability of advanced imaging modalities [20–22]. Another reason may be that pelvic surgery increased the probability of finding appendiceal fNEN [23]. Furthermore, we noticed that the population of patients diagnosed after 50 years old was larger than the younger and approximately accounted for four-fifths of fNENs.

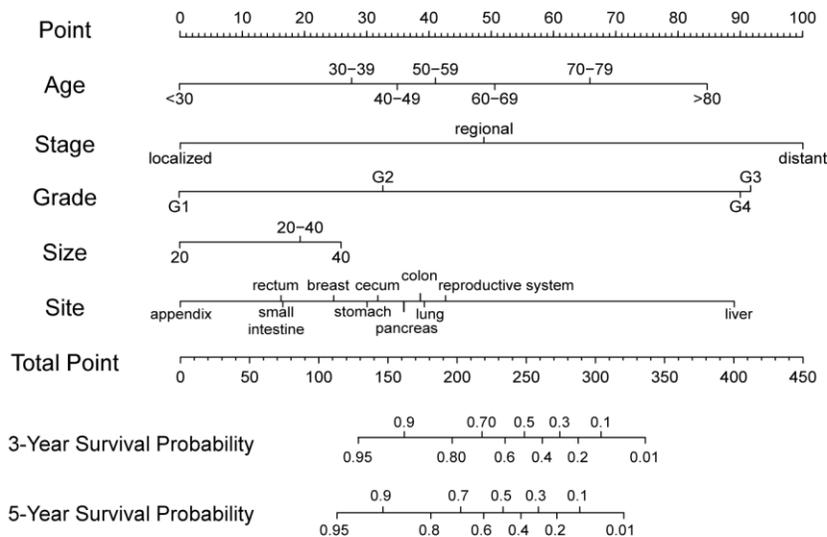
At the same time, the number of patients aged 50-59 was twice as many as patients aged 40-49 years old, indicating that menopause (about 50 years old) significantly affects the incidence.

Previous studies demonstrate an age-dependent pattern for nearly all pancreatic cancer risk factors [24]. A previous epidemiological survey of NENs also showed that a more significant growth of incidence was found in the older, suggesting that age has a huge impact on the morbidity of NENs [15]. Thus, considering the enormous effects of different ages and sites, we evaluated the incidence patterns according to site and detailed age groups. The frequency distribution of incidence by site and age corroborated our hypotheses that the occurrence of fNENs in different sites is partially age-dependent. Different from previous studies, appendiceal NENs were more diagnosed in women younger than 40 and the number decreased as people advanced in age [25]. The pelvic surgery made appendiceal NENs more frequent and the age of diagnosis is getting younger and younger [23]. Thus, appendiceal NENs in young women deserve more attention, corresponding screening and treatment strategies might be made for them [26]. Further analysis revealed that the upstart rectal fNENs play a major role in patients between 40-59 and pulmonary fNENs in patients over 60 years old, suggesting that appropriate screening time and site should be considered for different populations. The incidence of fNEN in the lung, pancreas, rectum, and small intestine has doubled after the age of 50, and the proportion of fNENs younger than 40 years old is the highest among appendiceal fNEN, which coincidentally corresponds to

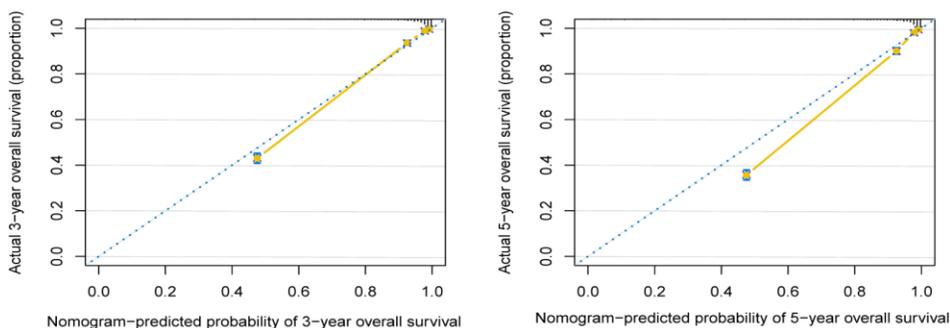
the weakest (menopause) and most vigorous (gestation period) period of female hormones. This age-dependent incidence pattern makes us pay attention to the role of female hormones in it. In reported small intestinal

NENs, the increased risk of mesenteric metastasis in women around menopause also presented the role of hormones in fNENs [27]. In a word, age differences in fNENs may be attributed to the effects of different

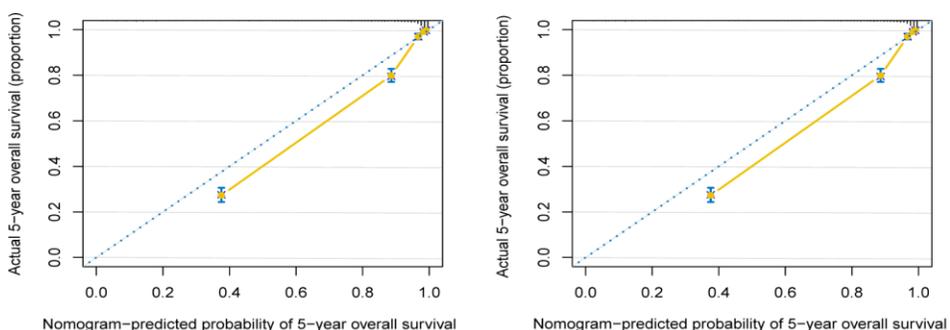
### A Survival prediction nomogram



### B Calibration plot in the training set



### C Calibration plot in the validation set



**Figure 5. Nomogram to predict the 3-Year and 5-Year survival probabilities of female neuroendocrine neoplasms (fNENs) patients and the calibration of the nomogram using the training and validation sets. (A)** Points for age, disease stage, tumor grade, tumor size, and primary tumor site are obtained by drawing a line upward from the corresponding values to the “Points” line. The sum of the points of these 5 factors is located on the “Total points” line, and a line projected down to the bottom scales determines the probabilities of 3-year and 5-year overall survival (OS). **(B)** Calibration plots of the nomogram for 3-year and 5-year survival probabilities in the training set. **(C)** Calibration plots of the nomogram for 3-year and 5-year survival probabilities in the validation set.

hormone levels on different organs. However, more investigations are required to explore whether and how hormone secretion status influences the fNENs in different sites.

The 5-years survival estimate for fNENs patients was 15.0 years, higher than that of reported overall NENs patients [14, 15]. Given the mismatching of diagnostic time, we cannot conclusively state that women have better prognoses. Different from the results of the whole NENs population, we found that fNENs in the rectum had the best median OS among site groups, a little longer than that in appendix [14, 15]. While the worst outcomes were shown in hepatic NENs. For women patients, NENs of breast and reproductive system deserve more attention, mainly because they are too rare to be checked timely. Similarly, we analyzed the relationship between survival, age, and site, finding that breast, reproductive system, and liver fNENs had the lowest 5-year survival rate in patients younger than 40, between 40-49, and over 50 years old, respectively. Therefore, clinicians should raise awareness of rare fNENs and carry out timely and effective treatment.

As reported, age, disease stage, grade, size, and primary tumor site were important predictors of survival outcomes [14, 15]. Our analyses did not observe a statistically significant difference in survival period among patients of different races and years of diagnosis, indicating better representativeness and applicability. Consistently, the disease stage had the greatest significance, contributing a maximum of 100 points. At the same time, age (85 points) and site (89 points) also had a great influence on survival, which was not observed in another nomogram whose age groups were simply divided [28]. More detailed division and higher weight of age made our nomogram model have higher predictive power [28, 29]. The need for precise analysis of clinical characteristics makes the use of more detailed age groups in large data-based studies a future research trend [24, 30]. As our nomogram's good performance and high compatibility were confirmed, it will provide a preliminary assessment for patient stratification and precision therapy, which would be more helpful for practicing clinicians. However, the treatments were not contained in the prognostic model because of the limitation of the database. The treatments for NENs include somatostatin analogue therapy, molecularly targeted agents (for example, everolimus and sunitinib), peptide receptor radionuclide therapy with Lutetium-177 DOTA-TATE (177Lu PRRT), chemotherapy, and surgery, which were not as detailed as we wished in it [5]. Despite all this, our nomograms still show a high accuracy, which could provide a preliminary prognostic evaluation for fNENs patients.

There were several limitations in our study. First, the use of the database had natural lag and potential bias, which may cause some discrepancies from the true incidence of NENs. Due to the limitations of accessible information, we took more consideration of baseline characteristics and lacked more detailed patient-level data beyond basic demographics and tumor characteristics. Then, we did not perform external validation with an independent cohort to further confirm the generalizability. However, the SEER database initially provided a comprehensive epidemiologic picture of fNENs, which helped us to get first-hand data for guiding clinical practice. The SEER database has its own stage and grade system, which differs somewhat from the latest proposed classification [31, 32]. And we look forward to the update of the SEER system that will provide more clinical information in the future.

## CONCLUSIONS

The incidence of fNENs has continued to rise from 2000 to 2018. The incidence and survival pattern presented obvious differences in various age and site groups, emphasizing the necessity of making specific screening strategies for patients of different ages. The poor prognosis of fNENs in uncommon sites, such as the breast, reproductive system, and liver also deserved more attention. The nomogram based on this data had been proven to be accurate and reliable, indicating the application for preliminary patient evaluation. However, we need to collect more clinical information further to improve the accuracy of the model in the future.

## Abbreviations

NENs: neuroendocrine neoplasms; fNENs: female neuroendocrine neoplasms; OS: overall survival; APC: annual percentage change; SEER: Surveillance, Epidemiology, and End Results; NHW: Hispanic, non-Hispanic white; NHB: non-Hispanic black; NHAPI: non-Hispanic Asian or Pacific Islander; NHAIAN: non-Hispanic American Indian/Alaska Native; HRs: hazard ratios (HRs); CI: confidence interval.

## AUTHOR CONTRIBUTIONS

Dr. Xu and Zhang had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Xiao, Xu, Zhang. Acquisition, analysis, or interpretation of data: Xiao, Xu, Zhang, Dai, Ouyang. Drafting of the manuscript: Xiao, Xu, Zhang. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Xiao, Xu, Zhang, Dai, Huang. Critical revision of the manuscript

for important intellectual content: Luo, Liu, Cao. Administrative, technical, or material support: Klein, Seal. Supervision: Luo, Liu, Cao.

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## CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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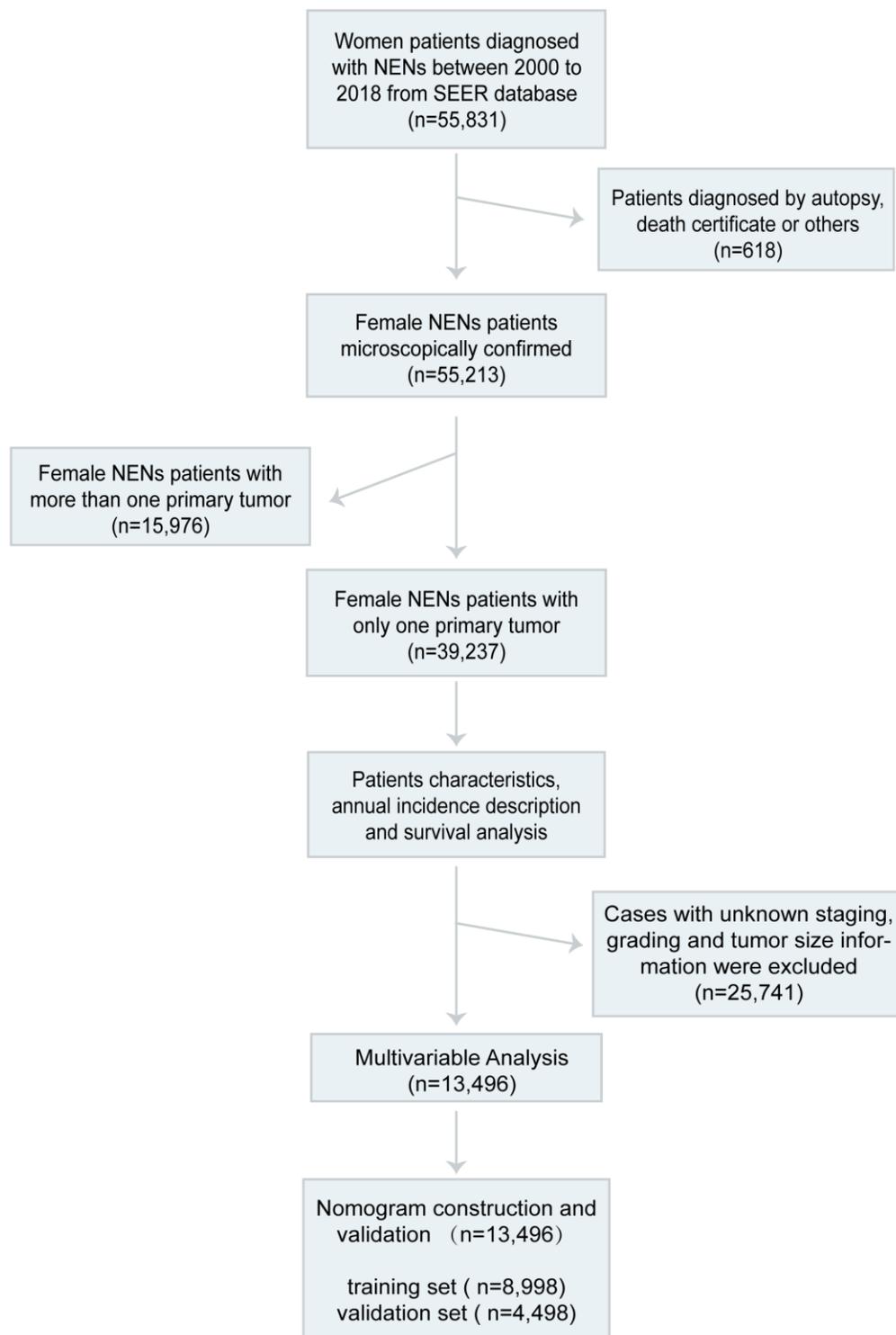
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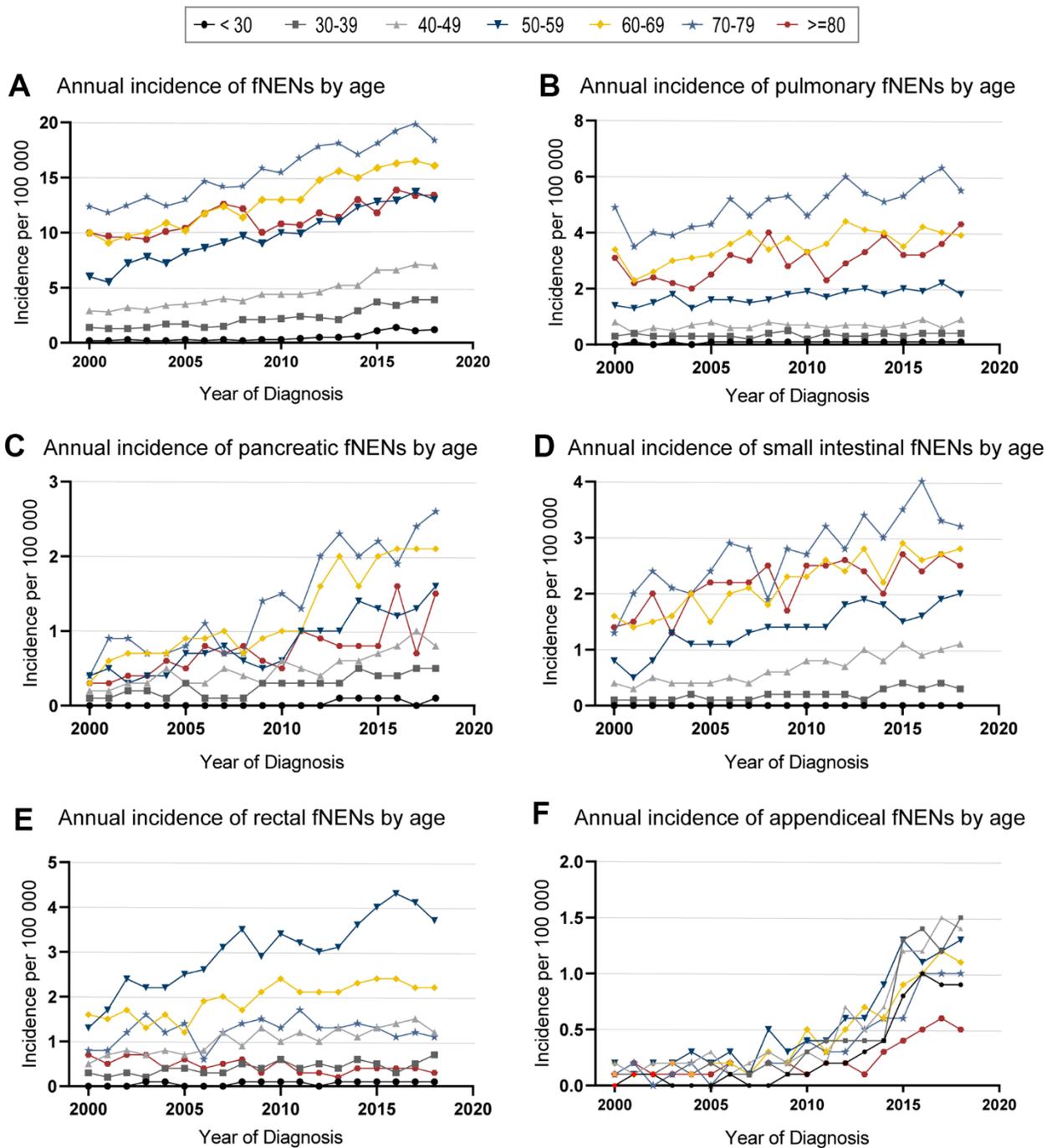
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## SUPPLEMENTARY MATERIALS

### Supplementary Figures

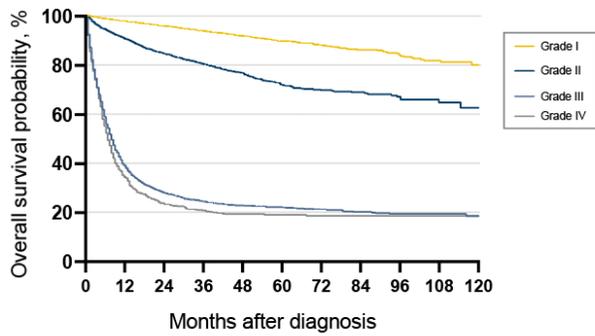


Supplementary Figure 1. Flowchart of patient selection and study design.

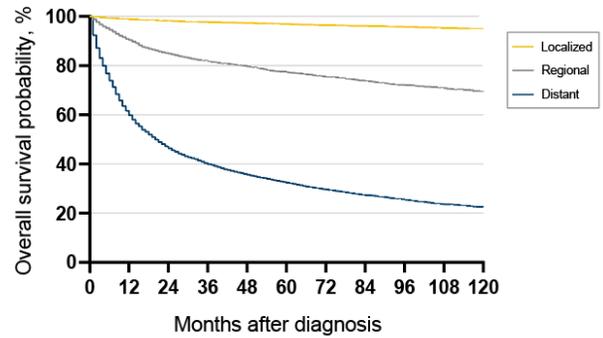


**Supplementary Figure 2. Incidence in total and common sites of female neuroendocrine neoplasms (fNENs) by detailed age.** The incidence on detailed age in all fNENs (A), pulmonary fNENs (B), pancreatic fNENs (C), intestinal fNENs (D), rectal fNENs (E), and appendiceal fNENs (F).

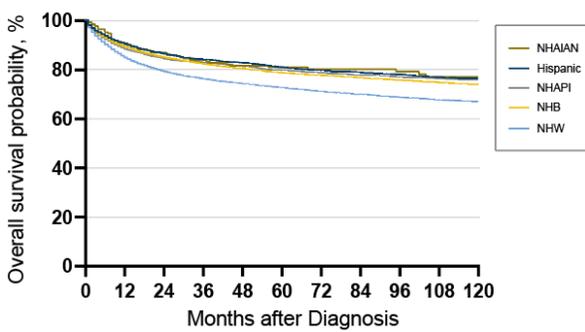
**A** Overall survival of fNENs by grade



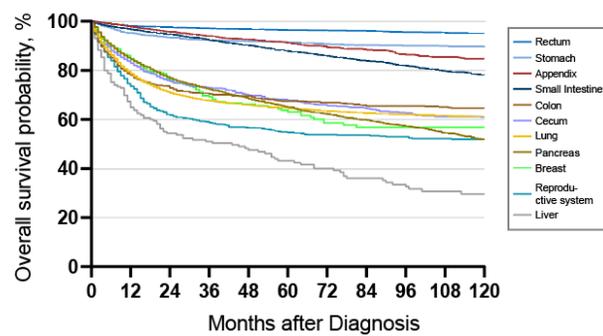
**B** Overall survival of fNENs by stage



**C** Overall survival of fNENs by race



**D** Overall survival of fNENs by site



**Supplementary Figure 3. The survival curve of fNENs by grade, stage, race, and sites.** The survival curve of fNENs by grade (A), stage (B), race (C), and primary site (D).

## Supplementary Tables

**Supplementary Table 1. Histologic codes from the international classification of disease for oncology, 3rd edition (ICD-O-3) used to identify neuroendocrine neoplasms (NENs).**

<b>NEN histology</b>	<b>ICD code</b>
Pancreatic endocrine tumor	8150/3
Insulinoma	8151/3
Glucagonoma	8152/3
Gastrinoma	8153/3
Mixed pancreatic endocrine and exocrine tumor	8154/3
VIPoma	8155/3
Somatostatinoma	8156/3
Carcinoid tumor	8240/3
Enterochromaffin cell carcinoid	8241/3
Enterochromaffin-like cell tumors	8242/3
Goblet cell carcinoid	8243/3
Mixed adenoneuroendocrine carcinoma	8244/3
Adenocarcinoid tumor	8245/3
Neuroendocrine carcinoma	8246/3
Atypical carcinoid tumor	8249/3

**Supplementary Table 2. The median OS and survival rate of female neuroendocrine neoplasms (fNENs) patients by detailed age and primary tumor site.**

Variables	Total	Lung	Rectum	Small intestine	Pancreas	Appendix	Stomach	Colon	Reproductive system	Cecum	Breast	Liver
<b>Total</b>	39237	8873	6958	5977	3637	3136	2746	1103	922	889	252	191
Median OS (Month)	180.1	163.8	213.7	184.3	161.3	187.2	195.4	120.0	105.3	133.4	150.6	79.4
<b>&lt;30</b>	1708	221	185	56	117	897	31	17	59	12	3	7
Median OS		NR	NR	NR	NR	NR	NR	NR	NR	NR	12.0	NR
3-Year SR		95.7	98.8	98.2	83.2	99.8	93.4	82.4	70.4	83.3	33.3	71.4
5-Year SR		95.7	98.8	98.2	77.7	99.4	93.4	82.4	70.4	83.3	33.3	71.4
<b>30-39</b>	2413	350	446	211	289	491	175	56	123	33	12	14
Median OS		NR	NR	NR	NR	NR	NR	NR	NR	NR	41.0	NR
3-Year SR		95.4	98.3	98.5	83.5	98.7	94.3	85.1	66.2	87.8	58.3	63.5
5-Year SR		94.7	97.7	97.8	76.0	97.0	92.5	80.4	62.2	87.8	48.6	63.5
<b>40-49</b>	5008	750	1122	733	527	551	405	129	193	90	36	15
Median OS		NR	NR	NR	212.0	NR	NR	NR	NR	NR	NR	143.0
3-Year SR		80.3	97.3	96.6	77.7	93.3	94.9	77.4	62.7	76.0	66.0	86.7
5-Year SR		78.0	97.0	93.9	71.2	89.4	94.6	73.3	59.6	72.1	62.8	79.4
<b>50-59</b>	9970	1728	3079	1417	870	569	658	330	210	224	46	38
Median OS		NR	NR	NR	148.0	NR	NR	NR	NR	NR	NR	37.0
3-Year SR		70.5	98.6	95.3	73.3	88.2	93.8	83.1	59.6	79.0	69.3	51.6
5-Year SR		67.8	98.3	92.4	65.9	83.8	93.6	81.9	56.6	75.0	60.8	36.6
<b>60-69</b>	9421	2571	1416	1599	931	368	682	226	171	229	66	44
Median OS		NR	NR	NR	114.0	NR	NR	NR	48.0	167.0	NR	23.0
3-Year SR		62.3	96.0	92.3	69.6	89.0	93.2	67.6	52.9	71.6	76.6	45.4
5-Year SR		59.5	95.4	87.6	62.4	84.0	92.2	65.7	48.1	67.2	69.6	42.9
<b>70-79</b>	7102	2263	557	1246	657	183	525	200	97	186	48	45
Median OS		69.0	NR	NR	80.0	NR	NR	24.0	10.0	62.0	180.0	21.0
3-Year SR		54.6	91.9	86.4	60.6	81.6	87.8	45.5	32.4	56.5	65.0	38.7
5-Year SR		51.0	89.5	80.8	54.8	78.5	86.7	40.0	28.0	49.4	58.2	23.2
<b>≥ 80</b>	3615	990	153	715	246	77	270	145	69	115	41	28
Median OS		36.0	NR	165.0	28.0	NR	NR	9.0	7.0	44.0	71.0	7.0
3-Year SR		50.0	80.7	79.5	46.2	80.5	76.9	37.9	27.8	54.1	57.8	15.8
5-Year SR		45.2	75.7	69.5	38.7	80.5	75.4	34.7	20.6	44.9	57.8	15.8

NR, means not reached; OS, overall survival; SR, survival rate (%).

**Supplementary Table 3. Baseline clinicopathological characteristics of fNENs patients in the training and validation cohorts.**

<b>Variables</b>	<b>All patients (n=13496) N (%)</b>	<b>Training set (n=8998) N (%)</b>	<b>Validation set (n=4498) N (%)</b>	<b>P-value</b>
<b>Age</b>				P>0.05
<50	3580(26.5)	2355(26.17)	1225(27.23)	
≥50	9916(73.5)	6643(73.83)	3273(72.77)	
<b>Race</b>				P>0.05
Hispanic	1806(13.38)	1223(13.59)	583(12.96)	
NHW	8872(65.74)	5900(65.57)	2972(66.07)	
NHB	1809(13.40)	1217(13.53)	592(13.16)	
NHAIAN	71(0.53)	46(0.51)	25(0.56)	
NHAPI	819(6.07)	535(5.95)	284(6.31)	
Unknow	119(0.88)	77(0.86)	42(0.93)	
<b>The year of diagnosis</b>				P>0.05
2000-2004	963(7.14)	647(7.19)	316(7.03)	
2005-2009	2022(14.98)	1341(14.90)	681(15.14)	
2010-2014	5266(39.02)	3501(38.91)	1765(39.24)	
2015-2018	5245(38.86)	3509(39.00)	1736(38.59)	
<b>Marital status</b>				P>0.05
Single	2647(19.61)	1765(19.62)	882(19.61)	
Married	6802(50.40)	4584(50.94)	2218(49.31)	
Divorced/widowed/separated	3269(24.22)	2139(23.77)	1130(25.12)	
Unknown	778(5.76)	510(5.67)	268(5.96)	
<b>Tumor Size (mm)</b>				P>0.05
≤ 20	7861(58.25)	5186(57.64)	2675(59.47)	
21-40	3286(24.35)	2232(24.81)	1054(23.43)	
≥ 41	2349(17.41)	1580(17.56)	769(17.10)	
<b>GRADE</b>				P>0.05
1	8952(66.33)	5934(65.95)	3018(67.10)	
2	2267(16.80)	1545(17.17)	722(16.05)	
3	1726(12.79)	1144(12.71)	582(12.94)	
4	551(4.08)	375(4.17)	176(3.91)	
<b>Disease stage</b>				P>0.05
Localized	7348(54.45)	4890(54.35)	2458(54.65)	
Regional	3493(25.88)	2386(26.52)	1107(24.61)	
Distant	2655(19.67)	1722(19.14)	933(20.74)	
<b>Primary tumor sites</b>				P>0.05
Appendix	1665(12.34)	1103(12.26)	562(12.49)	
Rectum	1752(12.98)	1163(12.93)	589(13.09)	
Small intestine	2660(19.71)	1767(19.64)	893(19.85)	
Pancreas	1840(13.63)	1217(13.53)	623(13.85)	
Lung	3328(24.66)	2234(24.83)	1094(24.32)	
Stomach	820(6.08)	542(6.02)	278(6.18)	
Colon	377(2.79)	241(2.68)	136(3.02)	
Cecum	467(3.46)	321(3.57)	146(3.25)	
Reproductive system	341(2.52)	237(2.63)	104(2.31)	
Breast	178(1.32)	126(1.40)	52(1.16)	
liver	68(0.50)	47(0.52)	21(0.47)	

NHW indicates Non-Hispanic White; NHB, Non-Hispanic Black; NHAIAN, Non-Hispanic American Indian/Alaska Native; NHAPI, Non-Hispanic Asian or Pacific Islander; mm, millimeter; Grade 1, Well differentiated; Grade 2, Moderately differentiated; Grade 3, Poorly differentiated; Grade 4, Undifferentiated, anaplastic.