Cardiovascular mortality risk among patients with gastroenteropancreatic neuroendocrine neoplasms: a registry-based analysis

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Research

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Abstract

Background

The research aimed to explore mortality patterns and quantitatively assess risks of cardiovascular mortality (CVM) in patients with primary gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs).

Methods

We extracted data from the Surveillance, Epidemiology and End Results (SEER) database for patients diagnosed with GEP-NENs between 2000 and 2015. Standardized mortality ratio (SMR) and the absolute excess risk were obtained based on the reference of general US population. The cumulative incidence function curves were constructed by all causes of death. Predictors for CVM were identified using multivariate competing risk model.

Results

Overall, 42027 patients were enrolled from the SEER database, of which 1598 (3.8%) died from cardiovascular disease (CVD). The SMR for CVM was 1.20 (95%CI: 1.14–1.26) among GEP-NENs patients. The cumulative mortality of CVD was the lowest in all causes of death, including primary cancer, other cancer, and other non-cancer disease. Furthermore, age of diagnosis, race, Hispanic origin, gender, marital status, year of diagnosis, grade, education level, region, SEER stage, primary site, surgery and chemotherapy were identified as independent predictors of CVM in GEP-NENs patients.

Conclusions

GEP-NENs patients have a significantly increased risk of CVM in contrast to the general population. Better cardioprotective interventions might be considered as a preferred method to protect heart for GEP-NENs patients.

Introduction

Neuroendocrine neoplasms (NENs) are a collection of fairly rare neoplasms, which used to be named as “carcinoid” on account of their heterogeneous and indolent clinical nature [1]. Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs) originate from neuroendocrine cells throughout the body constituting two-thirds of NENs [2]. In the past 40 years, the incidence of GEP-NENs has been steadily growing, with an increase of 3.65 times in the United States and 3.8–4.8 times in the UK [3]. The recently reported annual age-adjusted incidence of GEP-NENs is approximately 3.56/100,000 in the United States and 4.60/100,000 in England, respectively [4, 5]. Advanced in diagnostic endoscopy, physician awareness and treatment of cancers, the outcome of GEP-NENs patients had improved considerably, with 3- and 5-
year overall survival rates of 79.4% and 74.7%, respectively [6, 7]. Cardiovascular disease (CVD) has become one of the leading causes of non-cancer death [8].

A previous study reported that the cardiovascular mortality (CVM) had increased by 21.1% from 2007 to 2017 in global [9]. In 2016, approximately 17.9 million people died of CVD globally, accounting for 31% of the total global deaths, while roughly 9 million death caused by cancer [10, 11]. In the United States, Kochanek et al. reported that 647457 deaths arose from diseases of heart, more than 599108 deaths from primary malignant neoplasms in 2017 [12].

Prior studies have shown that patients with colorectal cancer and endometrial cancer have an 11.7 and 8.8 folds higher risk of CVM than the general population, respectively [13, 14]. Fang et al. have concluded that the risk of prostate cancer patients developing CVM in the first month and 7–12 months after diagnosis is 2.05 and 0.92 folds that of the general population, respectively [15]. Weberpals and colleagues have shown that the risk of CVM for breast cancer patients is 0.84 times that of the general population [16]. To sum up, the risk of CVM varies significantly among tumor patients depending on different primary sites and time after diagnosis compared with the general population. To our knowledge, there have been no reports focus on CVM of patients with GEP-NENs. Hence, we described the risk assessment and patterns for causes of death, and identified independent predictors for CVM in GEP-NENs patients in this study.

Methods

Data source

We extracted data of patients patients with primary GEP-NENs between 2000 and 2015 from the Surveillance, Epidemiology, and End Results (SEER) database using the SEER*Stat software (version 8.3.6) [17]. The SEER program, including incidence, survival and mortality data, is a system of population-based cancer registries sponsored by National Cancer Institute covering around 27.8% of the total US population (based on the 2010 census) [18]. The US mortality of the reference cohort (representing the general population) reported in the National Vital Statistics System also can be collected through the SEER program [19]. Ethical approval of this publicly available information provided by the SEER program was not required.

Study population

Patients histologically diagnosed with GEP-NENs at the first primary tumor aged ≥ 18 years were retrieved from the SEER database. The following International Classification of Diseases for Oncology, the third edition (ICD-O-3) histological codes were used: 8013, 8041–8044, 8150–8153, 8155, 8156, 8240–8046, 8249. The primary site codes were used for stomach (C16.0-C16.9), small intestine (C17.0-C17.9, C24.1), appendix (C18.1), colon (C18.0, C18.2-C18.9), rectum (C19.9, C20.9) and pancreas (C25.0-C25.9). Patients with a diagnosis at autopsy or death certificate only and variables (race, age and cause of death) with incomplete data were excluded (Fig. 1).
The main outcome of interest was CVM, defined by the six death causes in the SEER database (International Classification of Diseases, 10th Revision [ICD-10] codes): diseases of heart (I00-I09, I11, I13, I20-I51), hypertension without heart disease (I10, I12), cerebrovascular diseases (I60-I69), atherosclerosis (I70), aortic aneurysm and dissection (I71), and other diseases of arteries, arterioles, and capillaries (I72-I78) [20].

**Study Variables**

Data were summarized as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables, and number (percent) for categorical variables.

The variables involved in this study included age at diagnosis, attained age, year of diagnosis, gender, SEER stage (localized, regional, and distant), race, Hispanic origin, marital status, grade (well differentiated as grade I, moderately differentiated as grade II, poorly differentiated as grade III, and undifferentiated as grade IV), region (Midwest, West, South, Northeast), education level, mean household income, histologic subtype, primary site, surgery, chemotherapy, radiotherapy, cause of death and survival time.

Since there is no personal data on education level and household income in the SEER database, we used 2000 US Census data to obtain county-specific average educational level and household income [15]. Survival time refers to the interval from the diagnosis of cancer to the death of patients ascribed to any causes or the last day of the available survival information [21].

**Statistical analysis**

The relative risk of CVM for GEP-NENs patients was compared to all US residents and presented as the standardized mortality ratio (SMR) [22]. SMR is the ratio of observed to expected number of CVM [20, 21]. Expected numbers were calculated by multiplying the mortality rate in the reference cohort by the person years (PYs) in the cancer cohort [23]. The absolute excess risk (AER, per 10,000 PYs) was calculated as follows: AER = ([observed deaths - expected deaths] /PYs of observation) × 10,000 [20, 21]. CVM was described as the primary event of interest, while competing events refer to death causes by primary cancer, other cancer and other non-cancer. The crude cumulative incidence function (CIF) is used to express the probability of developing primary and competing events using Fine-Gray competing risk model [24, 25]. Multivariate competing risk survival analyses were performed to identify independent predictors of CVM. Data analyses were performed by R software (version 3.6.3). All tests are 2-sided, and P-value < 0.05 signified statistical significance.

**Results**

**Patient characteristics**

A total of 42027 qualified GEP-NENs patients were adopted for subsequent analyses. The mean age at diagnosis was 58.57±13.74 years and the median follow-up time was 54 (22-103) months. The majority of patients were White (74.2%), non-Hispanic (88.2%), married (56.4%), age at diagnosis ≥ 50 (77.6%),
had only one neoplasm (88.3%), lived in the Western region (48.8%) and with localized tumor stage (53.3%). The proportion of female patients (21281 cases, 50.6%) was similar to that of male patients (20746 cases, 49.4%). The most common primary site was rectum (30.0%), followed by small intestine (27.8%) and pancreas (14.1%). Histologic types for GEP-NENs consisted of neuroendocrine tumor (74.9%) and neuroendocrine carcinoma (25.1%). 32265 (76.8%) patients underwent surgery, 4337 (10.3%) patients received chemotherapy, only 985 (2.3%) patients underwent radiotherapy. Among 42027 patients, 1598 (3.8%) patients died of CVD, in which the main cause was diseases of heart (75.3%), followed by cerebrovascular diseases (16.9%) and hypertension without heart disease (4.2%). The baseline characteristics were detailed in Table 1 and 2.

**Standardized mortality ratio and absolute excess risk**

The SMR for CVM was 1.20 (95%CI: 1.14-1.26) and the AER was 12.63/10,000 PYs in GEP-NENs patients. In the subgroup analyses stratified by different variables, patients were Non-Hispanic; lived in the South, Midwest and West regions; aged at diagnosis ≤ 39, 40-44, 45-49, 55-59, 65-69, 70-74 and 85+; with attained age ≤ 39, 40-44, 45-49, 50-54, 65-69, 70-74 and 75-79; with primary site of stomach, small intestine and colon; with localized and distant stage; with latency of 0-1, 2-5 and 6-11 months; with unmarried, Grade III/IV, lower educational level, lower household income, no chemotherapy, and no radiotherapy had significantly elevated SMRs and increased AERs compared with that of the general population, regardless of race, gender, year of diagnosis, subtype and surgery (Tab.1).

**Cumulative mortality of CVD**

The results of CIF curves for all causes of death in GEP-NENs patients using Fine-Gray competing risk model were illustrated in Figure 2. The cumulative mortality (CM) of CVD was the lowest in all causes of death. At the follow-up time of 200 months, the CMs of CVD, primary cancer, other cancer, and other non-cancer disease were 9.4%, 12.3%, 16.9%, and 13.8%, respectively. In the early follow-up period, the highest CM was caused by primary cancer. The CMs of other cancer and non-cancer disease exceeded that of primary cancer at around 90 and 170 months after diagnosis, respectively.

In the subgroup analyses stratified by age at diagnosis, we observed that the CM of CVD steadily increased with the age at diagnosis (Tab. 3). The CM of CVD was the lowest in all causes of death in subgroups of aged < 50 years (3.1%) and 50-64 years (5.5%) (Tab. 3, Fig. 3A and B). In subgroups of aged 65-79 years and ≥ 80 years, the CM of CVD exceeded that of primary cancer at around 180 months and 120 months after diagnosis, respectively (Fig. 3C and D). In the subgroup analyses stratified by primary site, pancreas and small intestine NENs patients had the lowest (4.12%) and highest (13.26%) CM of CVD, respectively (Tab. 3). We observed that the CM of CVD was the lowest in all causes of death in subgroups of the primary site of colon (9.09%), appendix (4.84%) and pancreas (4.12%) (Tab. 3, Fig. 4A-C). In subgroups of the primary site of stomach and rectum, the CM of CVD exceeded that of primary cancer at around 160 months and 90 months after diagnosis, respectively (Fig. 4D and E). Interestingly, the CM of CVD in the subgroup of the primary site of small intestine was higher than that of primary cancer across all follow-up periods (Fig. 4F).
Predictors of cardiovascular disease deaths

We identified indicators associated with CVM in GEP-NENs patients using multivariate competing risk model (Tab. 4). We found that patients were Black (HR: 1.307; 95%CI: 1.160-1.472), non-Hispanic (HR: 1.370; 95%CI: 1.137-1.651); with older age (HR: 4.799; 95%CI: 4.313-5.341), unmarried (HR: 1.562; 95%CI: 1.410-1.173), no surgery (HR: 1.346; 95%CI: 1.188-1.519), no chemotherapy (HR: 1.610; 95%CI: 1.220-2.125) were independently associated with higher risks of CVM; meanwhile, patients were female (HR: 0.790; 95%CI: 0.717-0.869), diagnosed from 2005 to 2009 (HR: 0.798; 95%CI: 0.717-0.888) and 2010-2015 (HR: 0.575; 95%CI: 0.502-0.659); with regional (HR: 0.815; 95%CI: 0.714-0.931) and distant tumor stage (HR: 0.456; 95%CI: 0.382-0.544), grade III/IV (HR: 0.701; 95%CI: 0.533-0.923), college level > 25% (HR: 0.798; 95%CI: 0.706-0.902); lived in the Northeast region (HR: 0.813; 95%CI: 0.699-0.945); with primary site of appendix (HR: 0.698; 95%CI: 0.531-0.918), rectum (HR: 0.550; 95%CI: 0.468-0.646) and pancreas (HR: 0.506; 95%CI: 0.401-0.638) had independent association with lower risks of CVM.

Discussion

Multiple studies have confirmed that the risk of CVM among cancer patients varies considerably in different countries. In a population-based study of 21634 adult cancer patients, Ye et al. concluded that the risk of CVM has no significant differences between cancer patients and the general population in Australian (SMR: 0.97; 95% CI: 0.90–1.04) [26]. Oh et al. reported that compared with the general population in Korea, cancer patients have a lower risk of developing CVM (men, SMR: 0.73; 95% CI: 0.70–0.75; women, SMR: 0.83; 95% CI: 0.80–0.87), although they found a 20-fold increase in CVM among cancer patients from 2000 to 2016 [27]. Sturgeon et al. confirmed that the risk of CVM among 28 of types cancer patients was significantly increased by contrast with that of the general population in the United States, especially in the first year after diagnosis (SMR: 3.93; 95% CI: 3.89–3.97) [8]. A recent study based on the SEER database showed that 1680 (5.6%) NENs patients died from heart diseases and 545 (1.8%) NENs patients died from other CVD (hypertension without heart disease, cerebrovascular diseases, atherosclerosis, aortic aneurysm and dissection, and other diseases of arteries/arterioles/capillaries), with SMRs of 2.31 (95%CI: 2.20–2.42) and 2.36 (95%CI: 2.17–2.57), respectively [28]. Most NENs are primarily located in the GEP (67.5%) and bronchopulmonary system (25.3%) [29]; however, the 5-year overall survival rates between GEP-NENs (74.7%) and bronchopulmonary NENs (33.7%) patients were significantly different [7, 30]. These findings suggested NENs patients had various natures and characteristics depend on different primary sites. Hence, we focus exclusively on the GEP-NENs in the present study.

In this study, we comprehensively assessed the risk of all causes of death among more than 42 thousand GEP-NENs patients from the SEER database, and found the risk of CVM in GEP-NENs patients was 20% higher than that of the general US population (SMR: 1.20; 95%CI: 1.14–1.26).

According to the competing risk analyses, we found that the CM of CVD was the lowest among all causes of death including primary cancer, other cancer and other non-cancer disease.
In addition, we identified age of diagnosis, race, Hispanic origin, gender, marital status, year of diagnosis, grade, education level, region, SEER stage, primary site, surgery and chemotherapy were independent predictors of CVM in GEP-NENs patients.

NENs were previously known as carcinoid tumours, in which approximately 50% of patients developed carcinoid syndrome [31]. Around 60% NENs patients with carcinoid syndrome developed carcinoid heart disease (CHD) which was characterized by development of valvular dysfunction, in particular right heart failure [32]. In addition, several researches have found that NENs patients are prone to depression and anxiety [33, 34], which may aggravate state of cardiovascular physiology [15, 35]. These results may explain the high risk of CVM in patients with NENs to some extent.

In terms of the time after cancer diagnosis, we confirmed that GEP-NENs patients within the first two-month after diagnosis had the highest risk of CVM (SMR: 3.64; 95% CI: 3.05–4.30). This finding was similar to previous conclusions reported by Sturgeon et al. and Zaorsky et al. [8, 36]. Moreover, Ye et al. and Fang et al. showed that the recent diagnosis of cancer could be a major psychological stressor and lead to a negative effect on cardiovascular physiology [15, 26, 35]. These results suggested that psychiatric evaluation and psychological support could be indispensable for GEP-NENs patients with recent diagnosis of cancer. In terms of age at diagnosis, we observed that the CM of CVD steadily increased with the age at diagnosis. This phenomenon resembled previous findings reported by Weberpals et al. and Ye et al. [16, 26]. In general, death from primary cancer was the most common cause of death in cancer patients; however, the CM of CVD exceeded that of primary cancer in patients aged ≥ 65 during follow-up time (Fig. 3C and D). These results implied that surveillance efforts should not only include assessment of primary cancer but also control of modifiable risk factors for CVD in elderly cancer patients. In terms of primary site, we observed that pancreas NENs patients and small intestine NENs patients had the lowest (4.12%) and highest (13.26%) CM of CVD, respectively. One possible reason was that CHD occurs most frequently in small intestine NENs patients, accounting for 72% [32]. Another plausible explanation was that pancreas NENs patients had so advanced tumor stage that they might have not enough life expectancy to die of CVD [28, 37, 38], which may be explainable for the lower risk of CVM in patients with grade III/IV (HR: 0.701; 95%CI: 0.533–0.923) or distant tumor stage (HR: 0.456; 95%CI: 0.382–0.544).

The multivariate competing risk analysis was used to identify independent indicators of CVM in GEP-NENs patients in current study. We found that aged patients at diagnosis were inclined to die due to CVD (HR: 4.799; 95%CI: 4.313–5.341). Interestingly, patients with younger age at diagnosis (≤ 39 years) had the highest SMR 3.20 (95%CI: 1.93–4.99), which similar with the results reported by Zaorsky et al. [36]. Male patients had a high probability of CVM compare with female patients, as previous reports of colorectal cancer and non-Hodgkin's lymphoma [13, 39]. A plausible reason is that males have worse health behaviors, such as smoking and drinking, which were confirmed as independent risk factors of CVD [40–42]. Our study showed that Black patients were significantly associated with the higher CVM risk compared with other races. Although patients with different ethnicities had a difference in receiving cancer therapy in the United States, this difference alone cannot explain the discrepancies of cancer
patients in death due to non-cancer causes [43]. Hence, further investigations on this subject remained warranted. Patients with unmarried status showed propensity to die of CVD in contrast to married patients, as previously reported in non-Hodgkin's lymphoma [39]. A reasonable explanation was that married patients were more likely to feel cared for and encouraged and supported physically and spiritually in contrast to unmarried patients [44]. Other studies also had revealed that marriage could help to improve cardiovascular, endocrine, immune function and cancer prognosis [45-47]. Sturgeon et al. reported that individuals with low socioeconomic status were prone to have a high risk of CVM in cancer survivors [8]. In our study, patients with low education level commonly gave rise to higher risk of CVM, which was consistent with results of prior studies [15, 21].

In the present study, a majority (76.8%) of patients underwent surgery, 10.3% patients received chemotherapy, and only 2.3% patients received radiotherapy. Notably, multivariate analysis indicated that patients received chemotherapy had a reduced CVM risk compared with patients not received chemotherapy. This result seemed to be inconsistent with the known cardiotoxic effect of chemotherapy, but conformed with the finding reported by Low et al. [28]. A possible reason was that patients who received chemotherapy have not enough life expectancy to occur CVM events (median survival time: chemotherapy 18 months vs surgery 61 months). We concluded that patients without surgery had an increased CVM risk compared with patients received surgery, which was consistent to the results from prior studies [13, 14, 44]. In respect of radiotherapy, prior study reported that radiation-induced macrovascular damages accelerated age-related atherosclerosis and microvascular damages, and reduced capillary density [48], however, radiotherapy was not an independent predictor for CVM in our study. In the SEER program, radiotherapy was defined as the first-course radiation treatment but lack of detailed regimen. Therefore, further investigation is required to clarify the effect of radiotherapy on the risk of CVM in patients with GEP-NENs.

Limitations still exist in our study. First, some information associated with CVD were not available in the SEER registry, such as comorbidities, smoking and alcohol use, doses of radiotherapy and chemotherapy agents. Second, this study is a retrospective study, which might lead to a potential selection bias in the participants. Third, causes of death may be subject to misclassification ascertained from death certificates, and there was evidence indicating that causes on death certificates about CVM may be overestimated [49].

Conclusions

In conclusion, GEP-NENs patients were found to show an upward trend risk toward CVM in contrast to the general population, especially during the first two-month after diagnosis. The CM of CVD was the lowest among all causes of death including primary cancer, other cancer and other non-cancer disease. In addition, age of diagnosis, race, Hispanic origin, gender, marital status, year of diagnosis, grade, education level, region, SEER stage, primary site, surgery and chemotherapy were independent predictors of CVM in GEP-NENs patients. These results suggested that patients after diagnosis of GEP-NENs should be screened for CVD timely and undergo more extensive control of modifiable risk factors of CVM.
Abbreviations

CVM: cardiovascular mortality; GEP-NENs: gastroenteropancreatic neuroendocrine neoplasms; SEER: Surveillance, Epidemiology and End Results; SMR: Standardized mortality ratio; CVD: cardiovascular disease; NENs: Neuroendocrine neoplasms; ICD-O-3: International Classification of Diseases for Oncology, the third edition; ICD-10: International Classification of Diseases, 10th Revision; SD: standard deviation; IQR: interquartile range; PYs: person years; AER: absolute excess risk; CIF: cumulative incidence function.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analyzed in this study are available in the SEER repository and can be obtained from: https://seer.cancer.gov/data/.

Competing Interest

None.

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Authors' contributions

**SHS**: Writing-original draft, Investigation, Methodology, Data collection. **WW**: Resources, Visualization, Writing - review & editing, Conceptualization, Data curation, Validation, Supervision. **CYH**: Resources, Conceptualization, Data curation, Validation, Supervision.

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Tables

Table 1. Baseline features and standardized mortality ratios of cardiovascular mortality in patients with GEP-NENs.
| Age at diagnosis | Observed deaths (%) | Expected deaths | SMR (95% CI) | Excess Risk per 10,000 Persons (%) | Persons at risk |
|------------------|---------------------|-----------------|--------------|-----------------------------------|----------------|
| Total            | 1598 (100.0)        | 1335.17         | 1.20 (1.14-1.26) | 12.63 (100.0)                   | 208158.81      |
| ≤39              | 19 (1.2)            | 5.94            | 3.20 (1.93-4.99) | 7.04 (8.2)                       | 18551.09       |
| 40-44            | 22 (1.4)            | 11.93           | 1.84 (1.16-2.79) | 7.20 (5.7)                       | 13975.98       |
| 45-49            | 42 (2.6)            | 28.08           | 1.50 (1.08-2.02) | 6.82 (8.6)                       | 20403.40       |
| 50-54            | 85 (5.3)            | 80.47           | 1.06 (0.84-1.31) | 1.15 (17.0)                      | 39442.59       |
| 55-59            | 120 (7.5)           | 98.91           | 1.21 (1.01-1.45) | 6.62 (14.1)                      | 31881.72       |
| 60-64            | 148 (9.3)           | 125.91          | 1.18 (0.99-1.38) | 8.20 (13.0)                      | 26923.19       |
| 65-69            | 216 (13.5)          | 160.04          | 1.35 (1.18-1.54) | 25.18 (11.6)                     | 22225.34       |
| 70-74            | 248 (15.5)          | 196.42          | 1.26 (1.11-1.43) | 32.69 (8.6)                      | 15780.00       |
| 75-79            | 245 (15.3)          | 243.41          | 1.01 (0.88-1.14) | 1.49 (6.5)                       | 10680.86       |
| 80-84            | 249 (15.6)          | 239.02          | 1.04 (0.92-1.18) | 17.09 (4.2)                      | 5837.49        |
| 85+              | 204 (12.8)          | 145.04          | 1.41 (1.22-1.61) | 239.97 (2.6)                     | 2457.14        |
| Attained age     |                     |                 |              |                                   |                |
| ≤39              | 7 (0.4)             | 1.75            | 4.00 (1.61-8.24) | 4.71 (4.6)                       | 11150.06       |
| 40-44            | 15 (0.9)            | 4.18            | 3.59 (11.66)    | 1349 (9279.41)                   |                |
| Age Group | Cases (In%) | Mean (95% CI) | Standard Deviation | Median (95% CI) | Mean (95% CI) | Median (95% CI) |
|-----------|-------------|---------------|--------------------|-----------------|---------------|----------------|
| 45-49     | 24 (1.5)    | 12.04         | 1.99 (1.28-2.97)   | 8.10            | 2279 (5.4)    | 14764.25       |
| 50-54     | 54 (3.4)    | 36.68         | 1.47 (1.11-1.92)   | 6.44            | 4192 (10.0)   | 26890.15       |
| 55-59     | 85 (5.3)    | 69.65         | 1.22 (0.97-1.51)   | 4.61            | 5628 (13.4)   | 33270.87       |
| 60-64     | 117 (7.3)   | 100.68        | 1.16 (0.96-1.39)   | 5.13            | 6135 (14.6)   | 31835.12       |
| 65-69     | 160 (10.0)  | 126.93        | 1.26 (1.07-1.47)   | 12.12           | 6208 (14.8)   | 27279.73       |
| 70-74     | 219 (13.7)  | 154.03        | 1.42 (1.24-1.62)   | 30.87           | 4832 (11.5)   | 21043.16       |
| 75-79     | 243 (15.2)  | 187.69        | 1.29 (1.14-1.47)   | 36.37           | 3927 (9.3)    | 15210.00       |
| 80-84     | 245 (15.3)  | 223.75        | 1.09 (0.96-1.24)   | 21.06           | 2775 (6.6)    | 10086.80       |
| 85+       | 429 (26.8)  | 417.80        | 1.03 (0.93-1.13)   | 15.24           | 2738 (6.5)    | 7349.26        |
| Race      |             |               |                    |                 |               |                |
| White     | 1163 (72.8) | 1009.42       | 1.15 (1.09-1.22)   | 10.01           | 31176 (74.2)  | 153405.55      |
| Black     | 354 (22.2)  | 265.91        | 1.33 (1.20-1.48)   | 23.74           | 7411 (17.6)   | 37101.01       |
| Other     | 81 (5.1)    | 59.84         | 1.35 (1.07-1.68)   | 11.99           | 3440 (8.2)    | 17652.26       |
| Hispanic origin | Non-Hispanic | 1486 (93.0) | 1228.03          | 1.21 (1.15-1.27) | 13.93          | 37063 (88.2) | 185214.91 |
|           | Hispanic    | 112 (7.0)    | 107.14           | 1.05 (0.86-1.26) | 2.12           | 4964 (11.8)   | 22943.89       |
| Gender          | Male      | Female     | 1.14 (1.07-1.23) | 10.00 | 20746 (49.4) | 101446.47 |
|-----------------|-----------|------------|------------------|-------|-------------|------------|
|                 | 807 (50.5)| 791 (49.5) | 1.26 (1.17-1.35) | 15.13 | 21281 (50.6) | 106712.34  |
| Marital status  | Married   | 720 (45.1) | 1.00 (0.93-1.07) | -0.10 | 23712 (56.4) | 123646.41  |
|                 | Unmarried 734 (45.9) | 487.62 | 1.51 (1.40-1.62) | 39.29 | 14133 (33.6) | 62709.18   |
|                 | Unknown 144 (9.0) | 126.33 | 1.14 (0.96-1.34) | 8.10  | 4182 (10.0)  | 21803.21   |
| Year of diagnosis | 2000-2004 726 (45.4) | 627.07 | 1.16 (1.08-1.25) | 12.11 | 9143 (21.8)  | 81692.92   |
|                 | 2005-2009 567 (35.5) | 468.04 | 1.21 (1.11-1.32) | 12.66 | 12281 (29.2) | 78179.06   |
|                 | 2010-2015 305 (19.1) | 240.05 | 1.27 (1.13-1.42) | 13.45 | 20603 (49.0) | 48286.83   |
| Latency (months) | 0-1 137 (8.6) | 37.67 | 3.64 (3.05-4.30) | 147.80 | 2216 (5.3)  | 6720.98    |
|                 | 2-5 142 (8.9) | 68.03 | 2.09 (1.76-2.46) | 58.97  | 1762 (4.2)  | 12543.23   |
|                 | 6-11 125 (7.8) | 94.40 | 1.32 (1.10-1.58) | 17.73  | 1809 (4.3)  | 17263.08   |
|                 | 12-59 600 (37.5) | 580.04 | 1.03 (0.95-1.12) | 2.04   | 16636 (39.6) | 97633.01   |
|                 | 60-119 434 (27.2) | 410.15 | 1.06 (0.96-1.16) | 4.16   | 11781 (28.0) | 57388.46   |
|                 | 120+ 160 (10.0) | 144.88 | 1.10 (0.94-1.29) | 9.10   | 7823 (18.6) | 16610.05   |
| Grade           | I/II 362 (22.7) | 329.90 | 1.10 (0.99-1.22) | 5.51   | 16601 (39.5) | 58249.56   |
| III/IV     | Mean household income | Education level | Region     | Subtype | SEER stage |
|------------|-----------------------|-----------------|------------|---------|------------|
|            | 71 (4.4)              | 1165 (72.9)     | College level ≤ 25% | 976 (61.1) | 203 (12.7) |
|            | 53.70                 | 951.57          | College level > 25% | 622 (38.9) | 738 (46.2) |
|            | 1.32 (1.03-1.67)      | 1.22 (1.15-1.30)| Midwest    | 203 (12.7) | 203 (12.7) |
|            | 29.16                 | 14.82           | West       | 738 (46.2) | 738 (46.2) |
|            | 3183 (7.6)            | 22243 (52.9)    | South      | 433 (27.1) | 433 (27.1) |
|            | 5932.23               | 143977.02       | Northeast  | 224 (14.0) | 224 (14.0) |
|            |                       |                 | Midwest    | 203 (12.7) | 203 (12.7) |
| ≤ $50,000 USD | 1129 (70.7)           | 469 (29.3)      | West       | 738 (46.2) | 738 (46.2) |
| > $50,000 USD | 898.10               | 436.54          | South      | 433 (27.1) | 433 (27.1) |
|            | 1.26 (1.18-1.33)      | 1.07 (0.98-1.18)| Midwest    | 203 (12.7) | 203 (12.7) |
|            | 17.09                 | 4.45            | West       | 738 (46.2) | 738 (46.2) |
|            | 27540 (65.5)          | 14472 (34.4)    | South      | 433 (27.1) | 433 (27.1) |
|            | 135144.75             | 72944.13        | Midwest    | 203 (12.7) | 203 (12.7) |
|            |                       |                 | West       | 738 (46.2) | 738 (46.2) |
| NEC        | 264 (16.5)            | 2134 (13.0)     | NET        | 1334 (83.5) | 1334 (83.5) |
|            | 208.69                | 1126.48         | 1126.48    | 1126.48  | 1126.48    |
|            | 1.27 (1.12-1.43)      | 1.18 (1.12-1.25)| 1.20 (1.12-1.28) | 1.20 (1.12-1.28) | 1.20 (1.12-1.28) |
|            | 16.96                 | 11.82           | 11.75      | 11.75    | 11.75      |
|            | 10558 (25.1)          | 31469 (74.9)    | 22388 (53.3) | 22388 (53.3) | 22388 (53.3) |
|            | 32606.72              | 175552.09       | 125886.88  | 125886.88 | 125886.88 |
|            |                       |                 |             | Regional | Distant    |
|            |                       |                 | Region      | 316 (19.8) | 187 (11.7) |
|            |                       |                 | Distant     | 187 (11.7) | 187 (11.7) |
|            |                       |                 | 292.87      | 157.80   | 157.80     |
|            |                       |                 | 1.08 (0.96-1.20) | 1.19 (1.02-1.37) | 1.19 (1.02-1.37) |
|            |                       |                 | 5.93        | 11.87    | 11.87      |
|            |                       |                 | 7818 (18.6) | 8546 (20.3) | 8546 (20.3) |
|            |                       |                 | 39005.99    | 24586.25 | 24586.25  |
|                |        |      |      |      |      |
|----------------|--------|------|------|------|------|
|                | Unstage|      |      |      |      |
| Primary site   |        |      |      |      |      |
| Stomach        | 258(16.1) | 160.09 | 1.61 (1.42-1.82) | 49.03 | 4287 (10.2) | 19969.91 |
| Small intestine| 683(42.7) | 529.00 | 1.29 (1.20-1.39) | 25.57 | 11672 (27.8) | 60214.91 |
| Appendix       | 58 (3.6) | 46.12 | 1.26 (0.96-1.63) | 8.78  | 3272 (7.8)  | 13535.66 |
| Colon          | 173(10.8) | 146.15 | 1.18 (1.01-1.37) | 14.16 | 4256 (10.1) | 18959.30 |
| Rectum         | 330 (20.7) | 353.74 | 0.93 (0.83-1.04) | -3.11 | 12595 (30.0) | 76355.76 |
| Pancreas       | 96 (6.0) | 100.07 | 0.96 (0.78-1.17) | -2.13 | 5945 (14.1) | 19123.27 |
| Surgery        |        |      |      |      |      |
| Yes            | 1145(71.7) | 1062.40 | 1.08 (1.02-1.14) | 4.80  | 32265 (76.8) | 172182.46 |
| No             | 438 (27.4) | 261.23 | 1.68 (1.52-1.84) | 52.03 | 9316 (22.2) | 33977.78 |
| Unknown        | 15 (0.9) | 11.54 | 1.30 (0.73-2.14) | 17.31 | 446 (1.1) | 1998.57 |
| Chemotherapy   |        |      |      |      |      |
| Yes            | 60 (3.8) | 55.03 | 1.09 (0.83-1.40) | 4.43  | 4337 (10.3) | 11236.04 |
| No/Unknown     | 1538 (96.2) | 1280.14 | 1.20 (1.14-1.26) | 13.09 | 37690 (89.7) | 196922.77 |
| Radiotherapy   |        |      |      |      |      |
| Yes            | 13 (0.8) | 12.69 | 1.02 (0.55-1.75) | 1.22  | 985 (2.3)  | 2530.49 |
| No/Unknown     | 1585 (99.2) | 1322.48 | 1.20 (1.14-1.26) | 12.77 | 41042 (97.7) | 205628.32 |
I: Well differentiated, II: Moderately differentiated, III: Poorly differentiated, IV: Undifferentiated; Race: Other (American Indian & AK Native & Asian & Pacific Islander); Marital status: Unmarried (Single & Separated & Divorced & Widowed & Unmarried or Domestic Partner); Attained age was defined as the age of the patient at the time of death or end of follow-up.

Abbreviation: SMR, standardized mortality ratio; CI, confidence interval; AER, Absolute Excess Risk; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.

Table 2. The standardized mortality ratios of all causes of cardiovascular mortality in patients with GEP-NENs.

| CVD                                         | Observed deaths (%) | Expected deaths | SMR (95% CI)         | AER per 10,000 |
|---------------------------------------------|---------------------|-----------------|----------------------|----------------|
| Total                                       | 1598 (100)          | 1335.17         | 1.20 (1.14-1.26)     | 12.63          |
| Diseases of heart                           | 1204 (75.3)         | 1018.14         | 1.18 (1.12-1.25)     | 8.93           |
| Hypertension without heart disease          | 67 (4.2)            | 47.14           | 1.42 (1.10-1.81)     | 0.95           |
| Cerebrovascular diseases                    | 271 (16.9)          | 223.69          | 1.21 (1.07-1.36)     | 2.27           |
| Atherosclerosis                             | 9 (0.6)             | 12.13           | 0.74 (0.34-1.41)     | -0.15          |
| Aortic aneurysm and dissection              | 20 (1.2)            | 18.59           | 1.08 (0.66-1.66)     | 0.07           |
| Other diseases of arteries, arterioles, capillaries | 27 (1.7)          | 15.49           | 1.74 (1.15-2.54)     | 0.55           |

Abbreviation: CVD, cardiovascular disease; SMR, standardized mortality ratio; CI, confidence interval; AER, absolute excess risk.

Table 3. Cumulative mortality stratified by age at diagnosis and primary site at 200 months follow-up.
| Characteristics          | Cumulative morality of all causes of death |
|-------------------------|------------------------------------------|
|                         | Primary cancer | Cardiovascular disease | Other cancer | Other non-cancer disease |
| Age at diagnosis (years)| <50           | 9.58                  | 3.10         | 10.84                    | 6.94          |
|                         | 50-64          | 10.63                 | 5.47         | 15.13                    | 10.12         |
|                         | 65-79          | 14.90                 | 16.32        | 23.44                    | 21.71         |
|                         | ≥80            | 21.94                 | 25.89        | 22.36                    | 26.78         |
| Primary site            | Stomach        | 11.41                 | 12.56        | 15.49                    | 20.75         |
|                         | Small intestine| 4.74                  | 13.26        | 25.12                    | 18.42         |
|                         | Appendix       | 15.79                 | 4.84         | 10.99                    | 10.52         |
|                         | Colon          | 25.37                 | 9.09         | 18.96                    | 10.76         |
|                         | Rectum         | 2.92                  | 7.65         | 10.35                    | 10.07         |
|                         | Pancreas       | 41.81                 | 4.12         | 17.20                    | 11.47         |

Table 4. Multivariate competing risk analysis for predictors of cardiovascular mortality in patients with GEP-NENs.
| Characteristics                  | adjusted HR | 95% CI     | P    |
|---------------------------------|-------------|------------|------|
| Age at diagnosis (years)        |             |            |      |
| < 65                            | Ref         |            |      |
| ≥ 65                            | 4.799       | 4.313-5.341| <0.001|
| Race                            |             |            |      |
| White                           | Ref         |            |      |
| Black                           | 1.307       | 1.160-1.472| <0.001|
| Other                           | 0.784       | 0.626-0.982| 0.034|
| Hispanic origin                 |             |            |      |
| Hispanic                        | Ref         |            |      |
| Non-Hispanic                    | 1.370       | 1.137-1.651| <0.001|
| Gender                          |             |            |      |
| Male                            | Ref         |            |      |
| Female                          | 0.790       | 0.717-0.869| <0.001|
| Marital status                  |             |            |      |
| Married                         | Ref         |            |      |
| Unmarried                       | 1.562       | 1.410-1.173| <0.001|
| Unknown                         | 1.171       | 0.984-1.394| 0.076|
| Year of diagnosis               |             |            |      |
| 2000-2004                       | Ref         |            |      |
| 2005-2009                       | 0.798       | 0.717-0.888| <0.0001|
| 2010-2015                       | 0.575       | 0.502-0.659| <0.0001|
| Grade                           |             |            |      |
| I/II                            | Ref         |            |      |
| III/IV                          | 0.701       | 0.533-0.923| 0.011|
| Unknown                         | 1.116       | 0.985-1.265| 0.085|
| Education level                 |             |            |      |
| College level≤25%               | Ref         |            |      |
| College level>25%               | 0.798       | 0.706-0.902| <0.001|
| Mean household income           |             |            |      |
| ≤$50,000 USD                    | Ref         |            |      |
| >$50,000 USD                    | 1.024       | 0.895-1.171| 0.73 |
| Region                          |             |            |      |
| West                            | Ref         |            |      |
| Midwest                         | 1.011       | 0.870-1.176| 0.88 |
| South                           | 0.943       | 0.834-1.065| 0.34 |
| Northeast                       | 0.813       | 0.699-0.945| <0.01|
| Subtype                         |             |            |      |
| NET                             | Ref         |            |      |
| NEC                             | 0.984       | 0.842-1.150| 0.84 |
| SEER stage   | Localized | Ref       |
|--------------|-----------|-----------|
| Regional     | 0.815     | 0.714-0.931 | <0.01 |
| Distant      | 0.456     | 0.382-0.544 | <0.001 |
| Unstage      | 0.990     | 0.840-1.167 | 0.9   |

| Primary site | Stomach | Ref       |
|--------------|---------|-----------|
| Small intestine | 1.055  | 0.911-1.222 | 0.48  |
| Appendix     | 0.698   | 0.531-0.918 | 0.01  |
| Colon        | 0.844   | 0.698-1.020 | 0.079 |
| Rectum       | 0.550   | 0.468-0.646 | <0.001 |
| Pancreas     | 0.506   | 0.401-0.638 | <0.001 |

| Surgery      | Yes      | Ref       |
|--------------|----------|-----------|
| No/Unknown   | 1.346    | 1.188-1.519 | <0.001 |

| Chemotherapy | Yes      | Ref       |
|--------------|----------|-----------|
| No/Unknown   | 1.610    | 1.220-2.125 | <0.001 |

| Radiotherapy | Yes      | Ref       |
|--------------|----------|-----------|
| No/Unknown   | 1.514    | 0.881-2.602 | 0.13  |

I: Well differentiated; II: Moderately differentiated; III: Poorly differentiated; IV: Undifferentiated; Race: Other (American Indian & AK Native & Asian & Pacific Islander); Marital status: Unmarried (Single & Separated & Divorced & Widowed & Unmarried or Domestic Partner).

Abbreviation: HR, hazard ratio; CI, confidence interval; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma.