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Original Article

Increased incidence of early onset colorectal adenocarcinoma is accompanied by an increased incidence of rectal neuroendocrine tumors

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Abstract: Recent studies have reported an increasing incidence of early onset colorectal cancer (CRC). Few studies compared the changing incidence of CRC by the major histological type, adenocarcinoma and neuroendocrine tumors (NETs). Using data from the Surveillance, Epidemiology, and End Results Program (SEER), we identified CRC from 1992 to 2015 with site and histological codes. Standardized incidence rates of CRC by anatomical locations (proximal, distal and rectal colon) and histological types (adenocarcinoma, NETs and others) were calculated over calendar years. Annual percent changes (APC) and joint-point regression were further computed. A significant increase of cancers in the distal colon and rectum was observed in young populations (20-44 and 45-54 years) but not in the proximal colon. Further analyses found that the highest rise of rectal NETs was in the 45-54 years which contributed 53.47% to the total increase of rectal cancer. The APCs for NETs in the rectum were 2.9 (95% CI: -0.1, 6.0) and 6.1 (95% CI: 3.8-8.4) for 20-44 years or 45-54 years respectively. The increase of NETs in the rectum was still significant in the older than 55 years (APC=3.7, 95% CI: 2.8-4.7), although the total CRC in this group was decreasing. Incidence of NETs in the distal colon is not apparently changing. The increase of CRC incidence among young populations (age < 55) is mainly due to the increased incidence in the rectum and distal colon. Moreover, the increase of early onset cancer in the rectum could be ascribed to increased incidence of adenocarcinoma and NETs.

Keywords: Colon, rectum, neuroendocrine tumors, adenocarcinoma, incidence, early onset colorectal cancer, annual percent change

Introduction

Colorectal cancer (CRC) incidence has been declining in the United States (US) since the 1990s, in contrast to the increasing CRC incidence observed in other countries [1]. This difference is attributed to national screening efforts in the U.S., and the unique ability to diagnose and remove pre-neoplastic intraepithelial neoplasia (e.g., colorectal adenomas) at the time of screening with colonoscopy. However, members of our study team and others have reported a significant escalating incidence of colorectal cancer in young populations within the U.S. (namely early-onset CRC) [1, 2]. Obesity, diet, and lack of CRC screening in young populations are suspected as the major culprits for the escalation. Anatomically, colorectal cancer can be divided into cancer in the proximal colon, distal colon and rectum. Previous studies have found distinct etiology of CRC by anatomical tumor subsite location. Moreover, CRC histology is diverse, with adenocarcinoma being the major type, following by neuroendocrine tumors (NETs), gastrointestinal stromal tumors, lymphoma and others. Interestingly, NETs, previously named as carcinoid tumors, were likely regarded as benign tumors and they usually grow slowly over many years, although there are fast-growing forms [3]. One study has reported an increasing trend of NETs in the gastrointestinal (GI) tract [4], however beyond this study few others have reported on the incidence of NETs due to it being a rare con-

Table 1. ICD codes for identification of colorectal cancer by anatomical locations

Category	Anatomical location	ICDO3		SEER codes
Proximal colon	Cecum	C180	Excluding 9050-9055, 9140, 9590-9992	21041
	Ascending colon	C182		21043
	Hepatic flexure	C183		21044
	Transverse colon	C184		21045
	Splenic flexure	C185		21046
	Appendix	C181		21042
Distal colon	Descending colon	C186		21047
	Sigmoid colon	C187		21048
	Large intestine, NOS	C188		21049
		C189		
		C260		
	Rectum and Rectosigmoid junction		Excluding 9050-9055,9140,9590-9992	
Rectum	Rectosigmoid junction	C199		21051
	Rectum	C209		21052

Note: Appendix (21042) and large intestine, NOS (21049) were removed from the calculation of incidence by anatomical locations.

dition. No study has investigated whether the incidence of CRC by histology and by anatomical locations has changed over time. Using the Surveillance, Epidemiology, and End Results Program (SEER), we initiated a study to analyze the incidence of CRC, with particular focus on whether the changing pattern of CRC is attributed to histological subtype changes.

Methods

Study population

Colorectal cancer cases diagnosed in 1992 through 2015 were identified from the SEER (the Surveillance, Epidemiology, and End Results Program) which covers approximately 13.4% of the US population. SEER collected basic demographic information including age at diagnosis of cancer, gender, race/ethnicity etc. and tumors related information, e.g., the international Classification of Diseases Code (ICD), histological type, tumor stage etc. Cancer patients are residents from San Francisco/Oakland, Connecticut, metro Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, metro Atlanta, Alaska, San Jose/Monterey, Los Angeles, and rural Georgia. In this study, we only included population aged equal or older than 20. The international Classification of Diseases Code (ICD) codes was used for identifying tumor locations (ICD-0-3/WHO 2008). The site codes can be found at SEER website https://seer.cancer.gov/siterecode/icdo3_d01272003/ which we extracted and re-categorized based on proximal colon, distal colon and rectum in **Table 1**. Histological type were identified as 1) Adenocarcinoma/signet ring cell carcinoma: 8140, 8141, 8143, 8145, 8147, 8210, 8211, 8213, 8220, 8221, 8255, 8260, 8261, 8262, 8263, 8265, 8480, 8481, 8490; 2) NETs (neuroendocrine tumor or carcinoid): 8240, 8241, 8242, 8243, 8244, 8246, 8249; 3) Others: 8000, 8001, 8004, 8010, 8012, 8013, 8014, 8020, 8021, 8022, 8030, 8031, 8032, 8033, 8041, 8042, 8044, 8045, 8046, 8050, 8051, 8052, 8070, 8070, 8071, 8072, 8073, 8074, 8076, 8077, 8081, 8082, 8083, 8120, 8123, 8124, 8130, 8144, 8201, 8230, 8231, 8251, 8312, 8341, 8380, 8400, 8430, 8440, 8441, 8460, 8470, 8482, 8500, 8503, 8507, 8510, 8523, 8542, 8550, 8560, 8570, 8571, 8572, 8574, 8576, 8720, 8721, 8730, 8744, 8746, 8770, 8772, 8800, 8801, 8802, 8804, 8805, 8810, 8814, 8830, 8850, 8851, 8852, 8858, 8890, 8891, 8895, 8900, 8933, 8935, 8936, 8940, 8950, 8951, 8963, 8980,9100, 9120, 9133, 9473, 9540.

Statistical analysis

Age standardized incidence rates were calculated using 2000 US population as the standard. Crude incidence rates were computed in every five-year age group starting at 20 until 85+. The direct method was applied to calcu-

late the age-stratum specific, expected numbers of CRC cases based on the standard population. Standardized incidence rate was then computed by summation of the stratum-specific expected number of CRC cases divided by the total number of standard population in that period. The calendar periods were counted as every three years from 1992-1994 to 2013-2015. Incidences of cancers in the proximal colon, distal colon and rectum were specified respectively. In order to compare the incidence in the young population or in the older population, we further categorized the population into age younger than 45, 45-54 and older than 55 and calculated the age-standardized rates over calendar periods. The three age groups represent pre-menopausal (< 45), peri-menopausal (45-54) and post-menopausal (≥55) period because CRC has been associated with sex hormone factors, and incidences of CRC are different among groups. We also analyzed data based on race/ethnicity groups (data not shown except rectal NETs). The age-standardized incidence rate was expressed as number of cancer cases per 100,000 persons.

Annual percentage changes (APC) were calculated using incidence rates calculated in each year from 1992 through 2015. Joinpoint trend regression method developed by the SEER statistical methodology and applications branch was used to calculate the APC and average annual percent change (AAPC) [5, 6]. The point estimate of APC and AAPC and corresponding 95% confidence interval (CI) were further computed [6]. The Joinpoint Regression Program allows the user to analyze joinpoints and trend lines to test if changes over time are statistically significant. Annual percentage change (APC) is the change in incidence between two years divided by the initial incidence rate and multiplied by 100. Average annual percentage change (AAPC) is the culmination of all APCs within a time period or the APC from the beginning to end of the data's time period.

For sub histological type of rectal cancer (e.g., adenocarcinoma, NETs in the rectum) whose incidence increased apparently, we run a linear regression model to evaluate the contribution of increase to the total increase of cancer in the rectum. The contribution of sub histological type of cancer in the rectum was estimated as the slope of the subtype cancer divided by the slope of the total cancer in the rectum, and multiplied by 100.

We used the Statistical Analysis System (SAS9.4, SAS Institute, North Carolina) to perform data management and calculate standardized incidence rates. APC and joint-point regression was based on SEER Joinpoint Regression program, V4.7.0.0. Figures were plots using Microsoft Excel 10.

Results

In total 426 262 colorectal cancer cases were identified in SEER from 1992 through 2015. Among them, 218 430 are males and 207 832 are females. The average age of diagnosis is 68.67 (68.67+13.58). The basic characteristics are displayed in **Table 2**.

Cancer incidence in the proximal colon and distal colon

In the young age group (< 55 years), incidence of cancer in the proximal colon did not display significant changes over calendar years. A decreasing trend of adenocarcinoma in the proximal colon has been observed in patient-cases ≥55 (**Figure 1**), which makes up a considerable majority of the incidence that parallels the overall histology trend. Incidence of NETs in the proximal colon is relative low and no significant changes were detected (**Figure 1**).

In the distal colon, an apparent increased cancer incidence was observed in the younger age group (< 55 years), with a sharper increase in the youngest group (20-44 ages). In contrast, a significant downward trend was shown in the older age (≥55 years). Adenocarcinoma is the predominant histological type in the distal colon, and NETs are relatively uncommon (**Figure 2**).

The incidence range seems to be similar in the proximal and distal colon for the two younger age groups, with a range between 1.5-2 cases per 100 000 and 10-13 cases per 100 000 for 20-44 years or 45-54 years groups respectively (**Figures 1A**, **1B**, **2A**, **2B**). The 55+ years population have a lower incidence range for distal colon cancer (70 down to 30 cases per 100,000) compared to proximal colon cancer (100 down to 60 cases per 100,000). Like proximal colon cancer, adenocarcinoma makes of a

Table 2. The basic characteristics of colorectal cancer in SEER from 1992 through 2015

	Male		Female	
	Number	Age at diagnosis (years), mean+STD	Number	Age at diagnosis (years), mean+STD
Total	218 430	67.31+13.06	207 832	70.09+13.96
Adenocarcinoma	205 852	67.54+12.90	193 753	70.26+13.75
Neuroendocrine tumors (NETs)	6 381	57.61+12.21	6 246	58.24+13.13
Proximal colon	84 380	69.92+12.83	98 812	73.22+12.78
Adenocarcinoma	81 304	69.89+12.78	94 481	73.08+12.70
Neuroendocrine tumors (NETs)	882	64.30+13.28	1 112	66.15+13.56
Distal colon	61 724	66.80+12.54	53 528	67.93+14.12
Adenocarcinoma	60 027	66.79+12.48	51 754	67.79+14.03
Neuroendocrine tumors (NETs)	518	59.25+13.18	444	59.99+14.33
Rectum	72 326	64.70+13.18	55 492	66.61+14.61
Adenocarcinoma	64 521	65.28+12.96	47 518	67.35+14.31
Neuroendocrine tumors (NETs)	4 981	56.25+11.48	4 690	56.20+12.13

large majority of the incidence and parallels the overall trend for all four distal colon graphs.

Incidence of cancer in the rectum

Cancer in the rectum exhibited a significant increase in younger population (20-44 and 45-54 ages, **Figure 3**). Specifically, NETs incidence was increased in all age groups but a substantial increase was observed in 45-54 and the age ≥55 years group (**Figure 4**). The observed NETs incidence trend in the rectum had an apparent impact on the all incidence rate for the two younger age groups (**Figure 3A**, **3B**) which blunted the effect of incidence trend in the older or all ages group (**Figure 3C**, **3D**). In the older age group (≥55 years), the increase of NETs did not show influential impact on the total decreasing trend because the incidence rates of adenocarcinoma were much higher and dominated the major contribution (**Figures 3C** and **5**). Specifically, when we evaluated the increase of subtype of cancers to the total increase of rectal cancer in age group 20-44 years, we found that adenocarcinoma contributed 76.42%, while NETs contributed 26.74% to the total increase (**Figure 3A**). Furthermore, the contribution of NETs became more apparent in age group of 45-54 years, which NETs contributed 53.47% but adenocarcinoma only contributed 43.15% to the total increase of cancer in the rectum (**Figure 3B**). For age group of 55+ years, NETs still showed an increasing trend but it was difficult to discern because adenocarcinoma was the major subtype now and it decreased substantially (**Figure 3C**).

When examining the proportions of colorectal cancer by histological type, we also observed a significant increased proportion of NETs in the younger age groups (45-54 years), and the older age group (≥55 years) (**Figure 6**).

APC, AAPC and joint-point regression analysis on incidence of rectal cancer

As rectal cancer displayed a distinct pattern of incidence by histological types, we calculated annual percent change (APC) and did a joinpoint regression analysis (**Table 3**). For 20-44 years group, there is an overall increase (average annual percent change, AAPC: 2.5 (95% CI: 2.1-2.9)) in the rectal cancer from 1992 to 2015. This overall increase can be attributed to increasing adenocarcinomas with AAPC at 2.4 (95% CI: 1.9-2.8) and NETs at 2.9 (95% CI: -0.1, 6.0) throughout the entire calendar period, although the AAPC for NETs was not significant most likely due to the non-significant decrease from 1992 to 1995. The largest increase of NETs in this age group is from 1995 to 2001 with AAPC at (13.8, 95% CI: 5.2, 23.0).

In age group 45-54 years, an overall increase (AAPC 1.9, 95% CI: 1.6, 2.2) was observed from 1992 to 2015. Among them, adenocarcinoma had an AAPC at 1.0* (95% CI: 1.0* (0.7, 1.3) for the entire calendar period, while NETs has an AAPC at 6.1 (95% CI: 3.8, 8.4). A large increase (AAPC 10.6, 95% CI: 9.1, 12.2) from 1994 to 2007, followed by a smaller increase (AAPC 2.2, 95% CI: -0.4, 4.8) from 2007-2015.

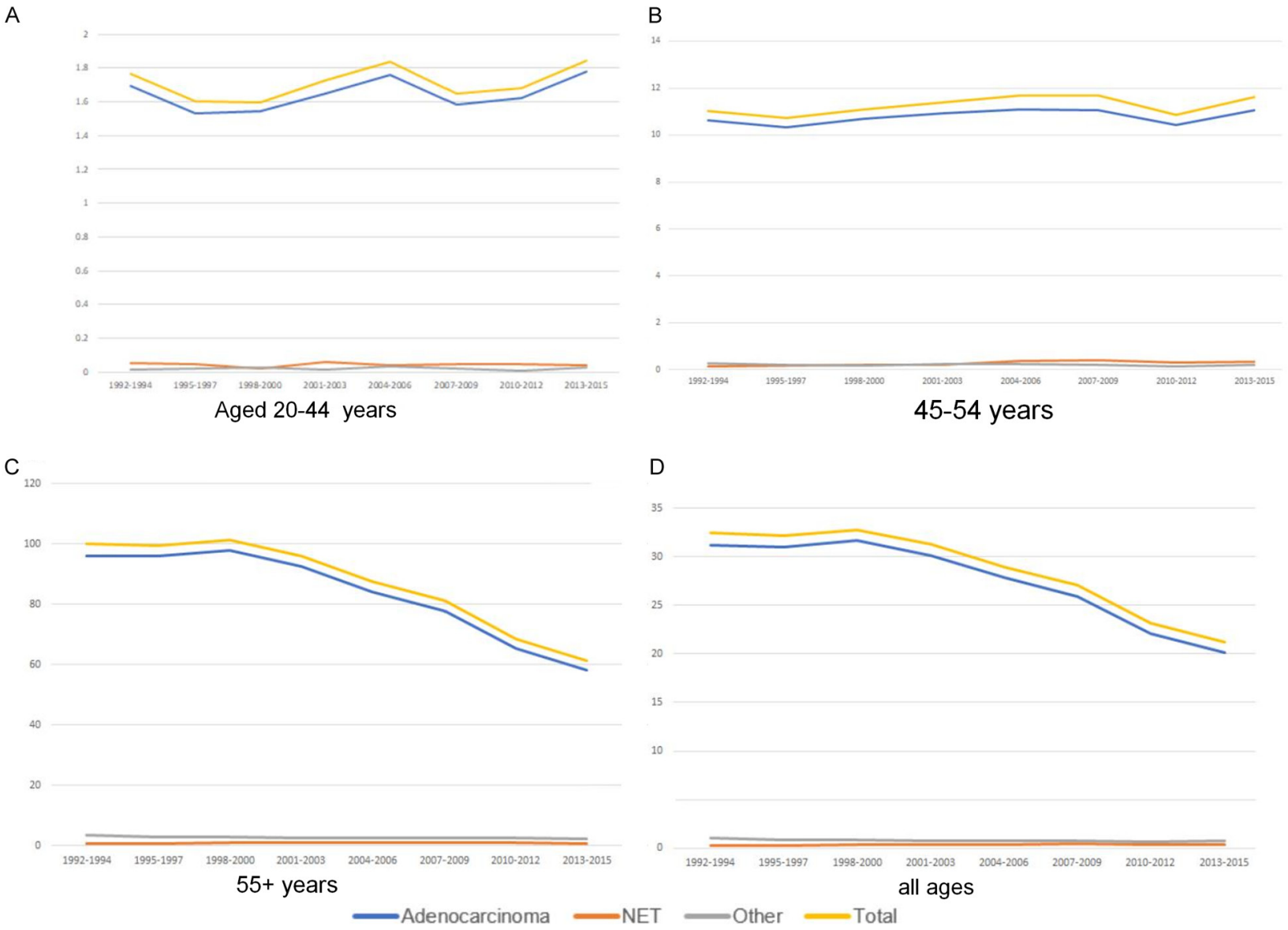

Figure 1. Incidence of cancer in the proximal colon by histology and by age groups.

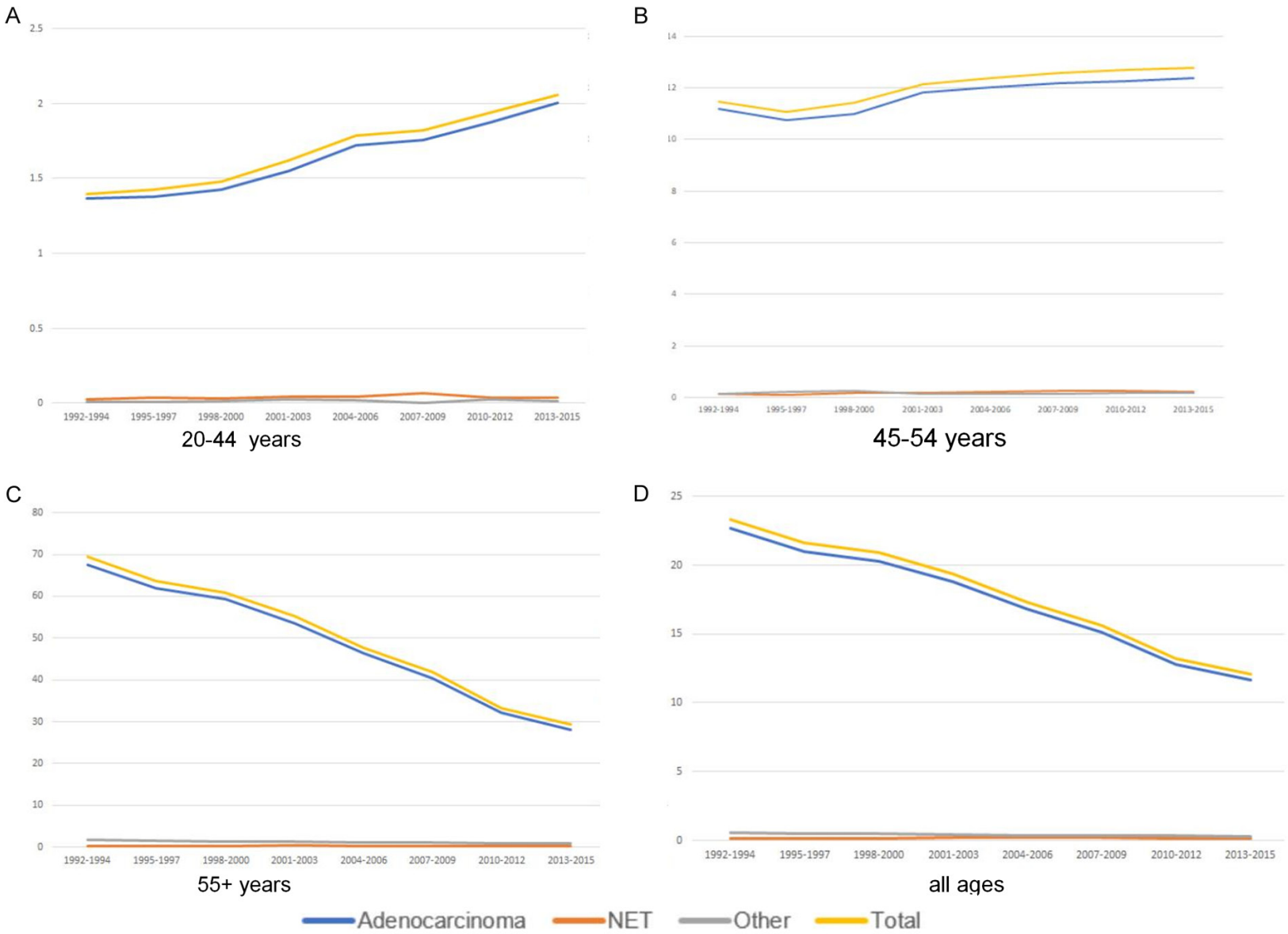

Figure 2. Incidence of cancer in the distal colon by histology and by age groups.

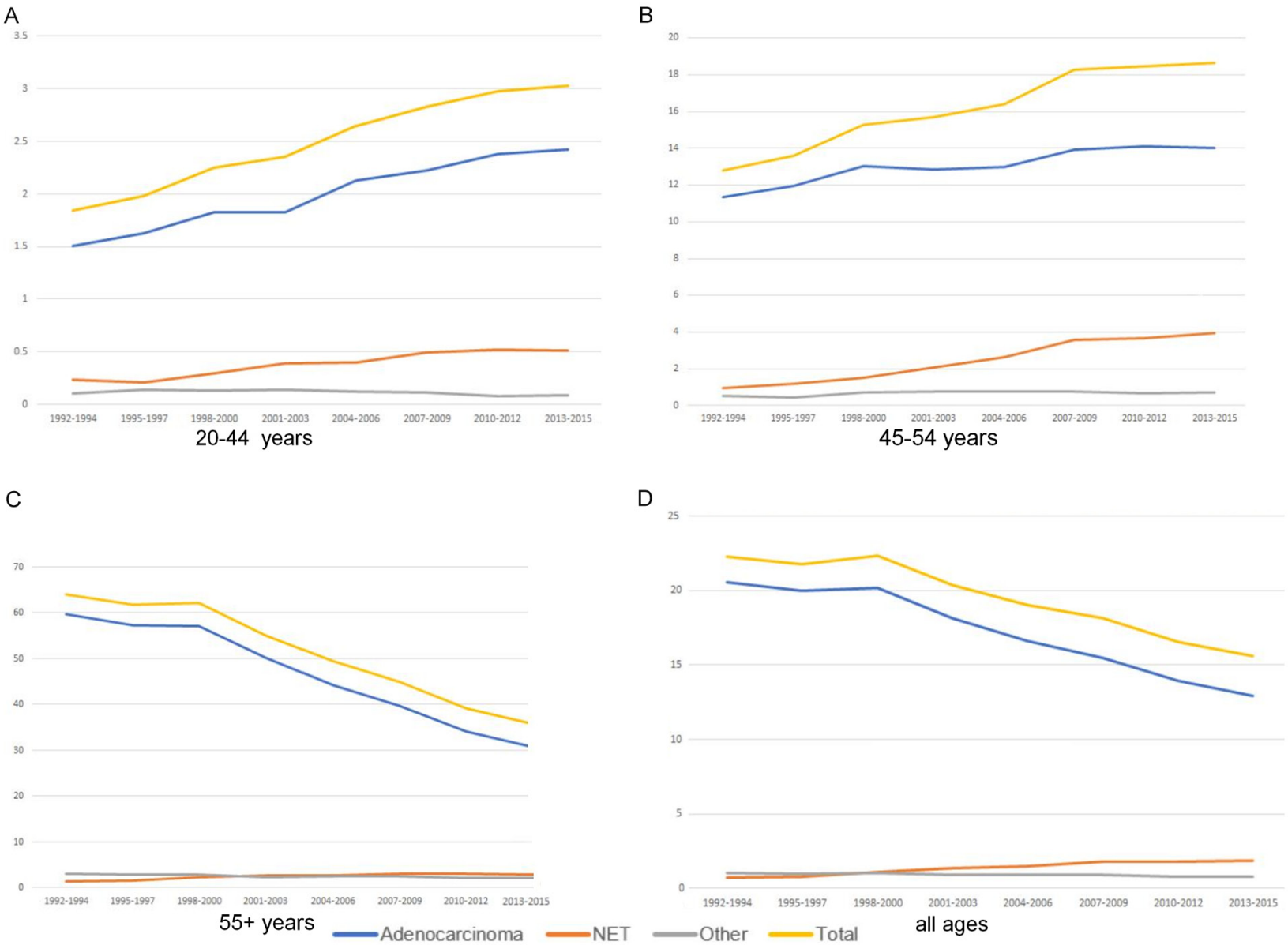

Figure 3. Incidence of cancer in the rectum by histology and by age groups.

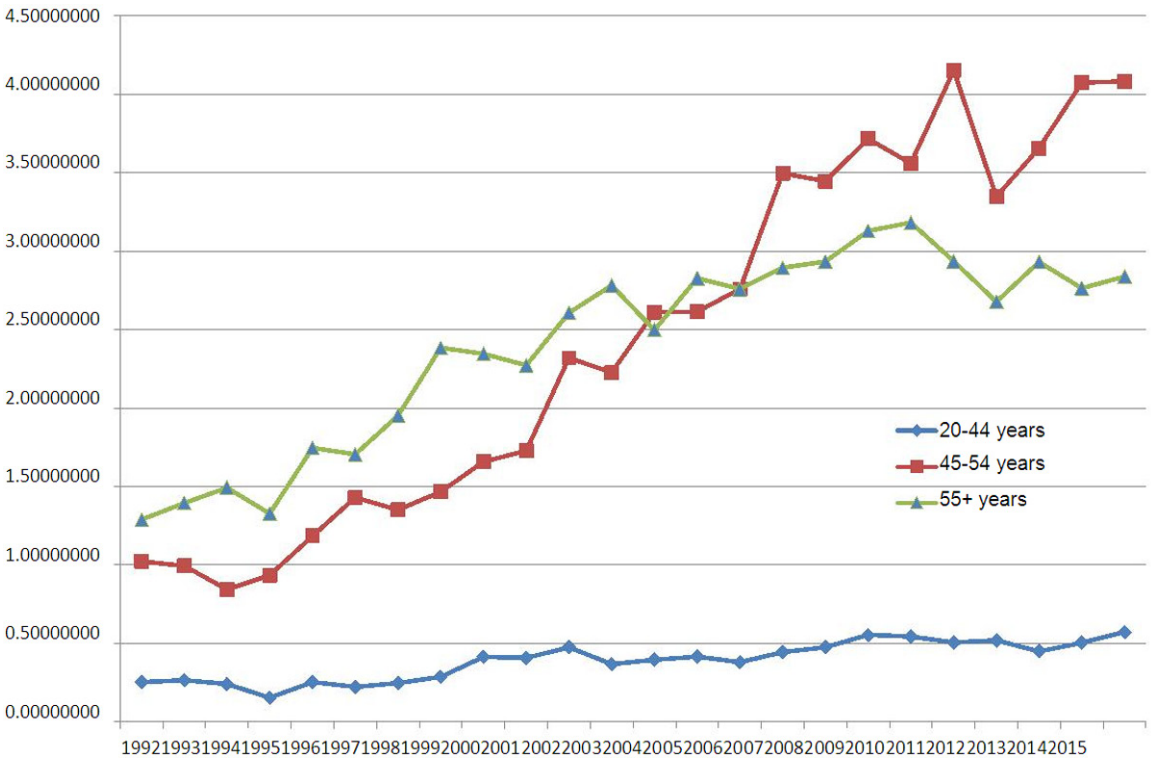

Figure 4. Incidence of neuroendocrine tumors (NETs) in the rectum by age groups.

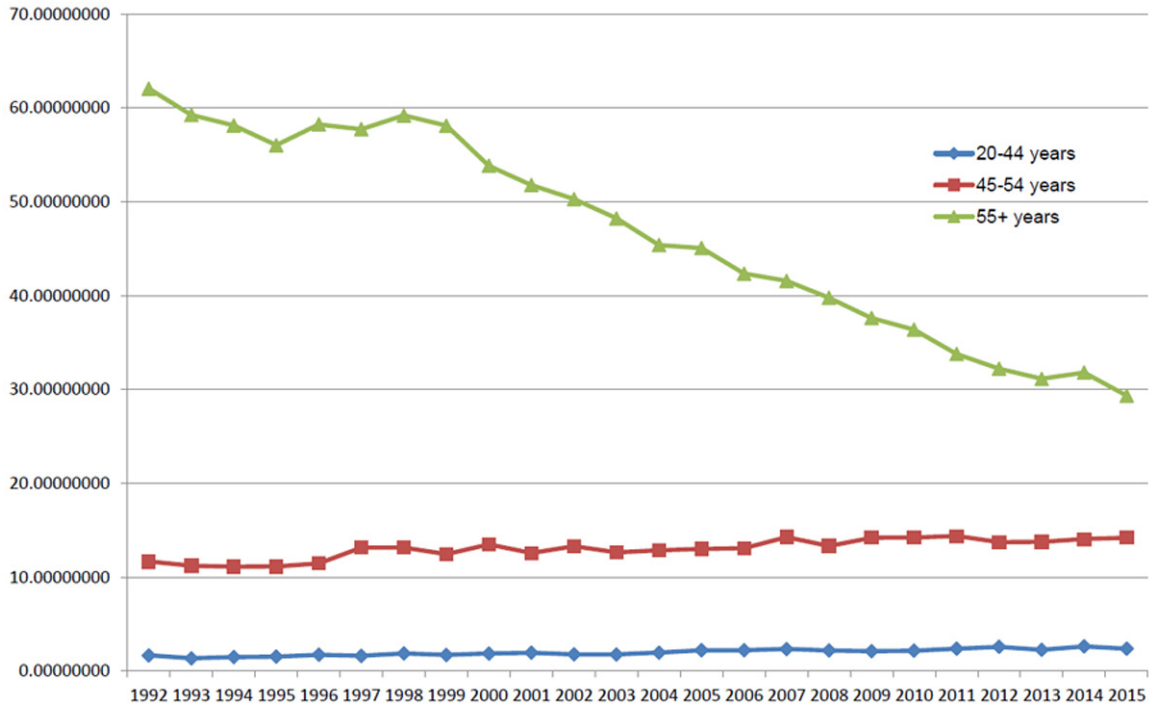

Figure 5. Incidence of adenocarcinoma in the rectum by age groups.

For the 55 years and older population, there was an overall decrease of AAPC at -2.8 (95% CI: -3.5, -2.1) from 1992-2015. This decrease came mostly from adenocarcinomas with an AAPC -3.2 (95% CI: -3.9, -2.4). Interestingly, a marked increase in NETs was observed in

Table 3. Trends in Rectal Cancer Incidence Rates by Age and Histology, United States, 1992-2015

	Trend 1		Trend 2		Trend 3		1992-2015 AAPC
	Years	APC	Years	APC	Years	APC	
20-44 years							
Adenocarcinoma	1992-2015	2.4* (1.9, 2.8)					2.4* (1.9, 2.8)
NETs	1992-1995	-13.0 (-26.9, 3.6)			2001-2015	2.2* (0.5, 3.8)	2.9 (-0.1, 6.0)
Other	1992-2015	-0.4 (-2.9, 2.1)					-0.4 (-2.9, 2.1)
Total	1992-2015	2.5* (2.1, 2.9)	1995-2001	13.8* (5.2, 23.0)			2.5* (2.1, 2.9)
45-54 years							
Adenocarcinoma	1992-2015	1.0* (0.7, 1.3)					1.0* (0.7, 1.3)
NETs	1992-1994	-6.1 (-25.7, 18.7)	1994-2007	10.6* (9.1, 12.2)	2007-2015	2.2 (-0.4,4.8)	6.1* (3.8, 8.4)
Other	1992-2003	5.2* (1.9, 8.6)	2003-2015	-1.1 (-3.8, 1.7)			1.9 (-0.1, 3.9)
Total	1992-2015	1.9* (1.6, 2.2)					1.9* (1.6, 2.2)
55+ years							
Adenocarcinoma	1992-1995	-3.0* (-5.7, -0.2)	1995-1998	1.7 (-3.9, 7.6)	1998-2015	-4.1* (-4.3, -3.9)	-3.2* (-3.9, -2.4)
NETs	1992-2003	7.5* (6.0, 9.1)	2003-2015	-0.4 (-0.9, 1.7)			3.7* (2.8, 4.7)
Other	1992-2015	-1.6* (-2.1, -1.1)					-1.6* (-2.1, -1.1)
Total	1992-1995	-2.7 (-5.4, 0.0)	1995-1998	1.8 (-3.6, 7.6)	1998-2015	-3.6* (-3.8, -3.4)	-2.8* (-3.5, -2.1)
All age groups							

*Asterisks indicate a significant change during this trend, as defined by a *p*-value of 0.05.

1992-2013 (APC 7.5, 95% CI: 6.0, 9.1), and the AAPC at 3.7 (95% CI: 2.8, 4.7) for the whole period from 1992 through 2015. When we analyzed the incidence of rectal NETs by race/ethnicity groups, we found a marked increase of incidence across all races aged equal or older than 45 (data not shown).

Discussion

A significant increase of colorectal cancer, especially rectal cancer was observed in the population aged younger than 55. Moreover, a remarkable increase of colorectal NETs was observed in all ages including the young population. In the population aged older than 55, a decreasing trend of CRC in total was observed but an increase of NETs was still apparent. The increase of NETs has a significant impact on the incidence of rectal cancer in the young population, especially in the age group 45-54 years, but not in the old population.

Recently, accumulating studies in US reported a continuous decrease of CRC since 1998 but an increase of incidence in young population [1, 2, 7-11]. Most of studies were based on SEER, or local cancer registries. Internationally, incidence of CRC exhibits an increasing trend in most of countries except a few, for example, New Zealand, Austria and US [12]. In US population, a continuous decreasing trend was found all race/ethnicity groups except Native Americans (data not shown). Studies reporting an increase of CRC in young population in US have attracted much attention [11]. Previous studies in the US have reached consensus about the decreasing incidence of CRC which is broadly attributed to CRC screening programs directed towards individuals over age 50. There is, however, no consensus about the causes of increase of CRC in young population. Many researchers believe this increase could be ascribed to low/no screening and the rising obesity prevalence in this population, or dietary patterns. Compared to CRC incidence (30-70 per 100 000 persons) in old population (≥55 years), incidence of CRC in 20-44 years (1.5-3 per 100 000 persons) and 45-54 years (13-19 per 100 000 persons) is low. The cost-effectiveness of screening in this population would not be high. Therefore, identification of reasons for the observed increase in early onset CRC is essential. As a result of the above issues, controversy has ensued, with various physician and advocacy groups calling for societies to lower their recommended age for CRC screening in average-risk populations. Others have advocated for adoption of low-cost CRC screening methods in young adults (i.e., fecal immunochemical testing, FIT). In 2018, the American Cancer Society (ACS) responded by lowering the recommended age for CRC screening in average risk individuals to age 45 (from 50) [13]. To date it is unclear to what extent the 2018 ACS recommendations are being adopt-

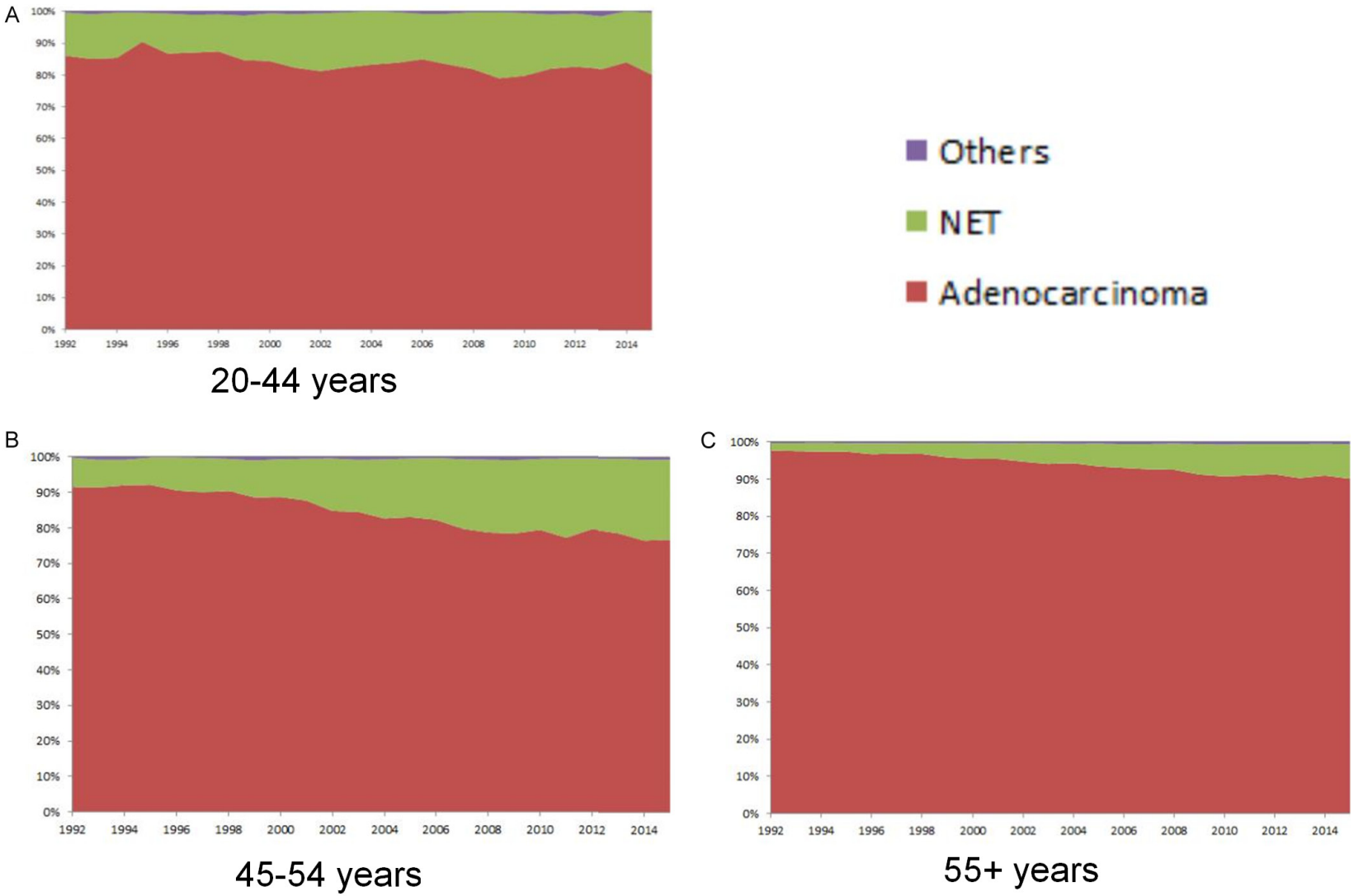

Figure 6. Proportion of histology of rectal cancer over years by ages groups. Note: NET neuroendocrine tumors.

ed, or if the change is adequate to address the rising incidence of early-onset CRC.

According to our analysis, increase CRC incidence in young populations was mainly attributed to rectal cancer. Moreover, there is an apparent histological disparity in rectal cancer compared to cancers in the proximal colon and distal colon. Although, adenocarcinoma still accounts largely for the observed increase of CRC in young populations, the influence of this trend by rapid escalation of NETs incidence cannot be ignored. NETs are a group of rare cancers accounting for 0.46% of gastrointestinal and bronchopulmonary malignancies [14]. Previous epidemiological studies have reported a rise of NETs incidence over the past decades [14-16]. Most of researchers or clinicians believe that such increase may partly reflect changes in diagnosis, improved detection through increasing use of imaging techniques or endoscopy. Changes in tumor biology have also been hypothesized but no data currently support it. Another point is about the mixed diagnosis of neuroendocrine carcinoma (NEC) and NETs. NEC is aggressive and high mitotic. Whether more NEC was included in the NETs group is unknown.

Nevertheless, the increase trend is due to changes of etiology or transition of diagnosis, colorectal NETs is an enigmatic malignancy that warrants further investigation. NETs have been regarded as an indolent cancer and diagnosis can be delayed up to 7 years [14, 15]. Current knowledge in NETs is still limited. It's important to note that there are no effective screening modalities for colorectal NETs. It lacks an identifiable precursor lesion, e.g., preneoplastic intraepithelial neoplasia, which would allow early diagnosis and removal akin to what is done for colorectal polyps (mainly colorectal adenomas). Screening modalities like FIT, fecal occult blood testing (FOBT), or stool DNA testing are not designed to detect colorectal NETs. Furthermore, high-grade NETs in the colon or rectum grow at a slow rate that they may be missed by colonoscopy or other screening.

Colorectal cancer data from the SEER is reliable with high validity. Histological type and anatomical locations were available for further categorization. We also have race/ethnicity group that help to identify the disparity of incidence among different populations. Weakness of the study cannot be ignored. SEER is not a nationwide cancer registry but only 13.4% of the total US population were covered. The sampling frame may affect the accuracy of the number of cancer cases. Diagnosis of cancers changed over time that may influence the validity of CRC identified in this study. Although we cannot ignore the weakness of SEER, it is still a reliable resource for registry of cancer in USA.

We conclude that the increased incidence of colorectal cancer in young populations is mainly due to increases in rectal cancer incidence, and more specifically that NETs incidence is rising in the rectum.

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Disclosure of conflict of interest

None.

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