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Forecasting Colorectal Cancer Trends in Young Patients: Eleven Years of Experience at the Indonesian National Referral Hospital

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Running Title: Trends of Colorectal Cancer in Indonesian Patients

Abstract

Objective: To obtain a trend analysis of CRC and provide a better understanding of clinicopathological and histopathological characteristics in Indonesian patients from a single center.
Methods: An 11-year retrospective cross-sectional study was conducted on 433 patients with colorectal cancer (CRC). Trend analyses were done using Joinpoint regression and the regression predictive fit model. The patient's characteristic data were calculated using Chi-Square and nonparametric tests in SPSS.
Results: The mean age of patients was 55.04±13.4, the male: female ratio was 1.22:1, and 33.3% of these patients were <50 y.o. The left colon and the rectum were the most commonly affected sites, and most cases had tumor size ≥5 cm. Exophytic tumor, adenocarcinoma, good differentiation, pT3, pN0, inadequately dissected nodes, LNR1, M0, negative lymphovascular invasion (LVI), and absence of perineural invasion (PNI) were the most common pathologic features. Most patients had an early CRC stage. Significant differences between young and old patients are observed only in the histological subtypes, LNR and PNI.
Conclusions: Epidemiological trends of CRC cases in Indonesian patients are increasing, and young-age CRC is more worrisome in clinicopathological features. The annual percentage change (APC) of CRC incidence increased significantly both in young and elderly patients (16.08% vs. 9.85%); in the colon and rectum only. Forecasts for the next five years using fit-model regression analysis found a significantly high number of patients, particularly in the colon.

Keywords: clinicopathological characteristics, colorectal cancer, histopathological characteristics, Indonesia, retrospective analysis, young onset, trend analysis.

Strengths and limitations of this study

- This study is the first report of CRC cases with long span coverage time from the country.
- This study provides a trend analysis and forecasting model of CRC in Indonesia.
- Data originated from single institution of national referral hospital.

Introduction

Gastrointestinal cancers are one of the most reported cancers in the world. Colorectal cancer (CRC) is the fourth most common cancer globally, and its incidence is rising, especially in developing nations.[1] CRCs are usually diagnosed through an endoscopic biopsy or polypectomy. Microscopic

examination is used to search for invasions. In the new era of personalized medicine, the role of anatomical pathologists has been dramatically expanding. Their role is no longer limited to providing histopathologic diagnosis but also assessing staging, margins, and prognostic parameters that can only be made available by microscopic examinations such as tumor grade, lymphovascular invasion (LVI), and perineural invasion (PNI). Further research about the pathological characteristic of CRC is essential for treatment approaches and policymaking.

Moreover, recent longitudinal studies have reported increased incidences of CRC in young populations below the age of 50 years worldwide, especially in high-income countries[2,3] and changing trends in CRC epidemiology in terms of clinical profile, histopathological profile, prognosis, and therapeutic approach.[4] In 2030, more than 1 in 10 colon cancer and nearly 1 in 4 rectal cancer cases are projected to be diagnosed in this age group for whom routine screening is currently not recommended.[5] This phenomenon is presumably due to rapid changes in lifestyle and diet and genetic alterations in high-risk people. A study in the United States concluded that CRC incidence in younger patients (20-40 years) increased by 17%. Similar trends have been observed in several Asian countries, including China, Japan, India, and South Korea, where a steep increase in young-onset CRC has been reported.[2,6] Being a critical issue in Asia, where the incidence of colorectal cancer is abundant in its Eastern part, CRC needs a better epidemiology perspective from another part of Asia, i.e., its southeastern part, especially Indonesia. Furthermore, in the population below 50 years, CRC shows a rising incidence and appears to display a more aggressive phenotype with unique genetic profiles, critical differences in somatic gene mutations, and gene methylation.[7]

However, to our knowledge, no previous comprehensive study on CRC clinical and histopathological characteristics and trend analysis of CRC in Indonesia as a Southeast Asian country has been published. Furthermore, distinct molecular carcinogenesis of CRC is discovered in Indonesia, as mentioned in a previous study.[8] These reasons support us to conduct a study to delineate the circumstances of CRC trend between 2009-2019 in young adults, defined as adults below 50 years old, compared to elderly populations for colon, rectal, and colorectal location. We also aimed to present a better view of clinicopathological and histopathological characteristics of CRC in Indonesian patients.

Materials and Methods

This retrospective cross-sectional study was conducted at the Dr. Cipto Mangunkusumo Hospital, Jakarta, to analyze colorectal cancer data from 2009-2019 using anatomical pathology archives and hospital medical records. Ethical approval (KET-139/UN2.F1/ETIK/PPM.00.02/2020, protocol number: 10-11-1416) was obtained from our institution. Data from 2020 were not included to avoid bias due to the COVID-19 pandemic impact in which CRC patient numbers coming to the hospital decreased. Patients who had a diagnosis of CRC based on ICD-O topography and morphology were included in the study. Patients with incomplete medical records were excluded. Age, sex, primary site, proximal and distal site of colorectal tumor, side involvement, size, and metastasis were recorded from the hospital medical records.[9] Young age was defined as under 50 years old, agreeing with previous studies.[10] The pathology specimens for each patient were examined under the microscope by two independent pathologists who recorded the histopathology characteristics that consisted of pathological tumor staging, histological subtypes, growth pattern, tumor grade, LVI, and PNI. We evaluated the number of dissected lymph nodes (LNs) in agreement with cancer studies and WHO guidelines, with a minimum of 12 LNs taken for each case.[11-13] Along with LNs, we also calculated the lymph node ratio (LNR) as the number of positive LNs divided by the total number of LNs examined. This parameter was introduced as a significant predictor of

survival in other malignancies and then classified the LNRs into subgroups according to the following quartiles: <0.05 (LNR1), 0.05-0.20 (LNR2), 0.20-0.40 (LNR3), and 0.40-1.00 (LNR4).[14]

The tumor site was defined as the location where the primary tumor originated. Right-sided tumors originate from the caecum, ascending colon, and hepatic flexure. Meanwhile, left-sided tumors originate from the transverse colon, spleen flexure, descending colon, sigmoid colon, and rectum. Proximal CRC originated from the caecum, ascending, and transverse colon. Meanwhile, distal CRC primarily occurs in the descending colon, sigmoid colon, and rectum.[9] Tumor size was defined as the largest dimension of three-dimensional tumors, classified into two groups: <5 cm and ≥5 cm. Metastasis was defined as distant metastasis confirmed by radiography or pathology diagnostic procedure. Pathological staging was based on the World Health Organization (WHO) guideline and AJCC 8th Edition.[12,13] Based on subtypes, a tumor was classified into adenocarcinoma not otherwise specified (NOS), mucinous adenocarcinoma, and signet-ring cell carcinoma variant. Advanced stage tumors are tumors with pT3-T4-stage or pTNM staging III-IV. The tumor growth pattern was classified into exophytic, endophytic, ulcerative, and linitis plastica.[15] Tumor grade was classified as well-differentiated, moderate, and poorly differentiated, according to a WHO classification based on the percentage of gland formation in the tumor mass.[12] LVI and PNI were defined as the occurrence of each parameter in at least one slide of the pathology specimen sample.[16]

Data were then recorded and processed using SPSS v.25.0 statistical software with Chi-Square and its alternative test (Fisher's exact test, Kruskal-Wallis, and Mann-Whitney. Analysis was performed for the young and the old patient's group for clinicopathological and histopathological characteristics. Incidence trends were quantified using Joinpoint regression (version 4.9.0.0; National Cancer Institute).[17] We also performed linear and non-linear regression generating models to predict the increasing trend of colorectal cancer cases in the next five years, then assessed their significance slope using the ANOVA test. P-value <0.05 with a 95% confidence interval (CI) for probability was considered significant.

Patient and public involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Results

Age groups in **Table 1** demonstrated that the highest proportion of CRC was in 51-60 y.o, the mean age was 55.04 ± 13.4 y.o, with females younger than males. The mean age of the young population was surprisingly very young (39.65 ± 6.87 y.o). The proportion of young patients in these centers reached 33.26% (n=144) of the total incidence (n=433). In our center, rectal and colon cancer were similar in number (50.3% vs. 49.7%), and the left-sided tumor was still the highest in proportion (82.9%). Among colon cancer, the sigmoid is the most prevalent location. Most tumor sizes were equal to more than 5 cm (61%), with brown color being dominant. Assessing distant metastasis, around 4.2% of the cases developed metastasis.

Table 1. Clinicopathological Characteristics of Tumor Between Young and Old Patients

Characteristics	Mean ± SD or Ratio	Young (<50 y.o) (n=144)		Old (≥50 y.o) (n=289)		Total (n=403)		p-value
		n	%	n	%	N	%	
Age Groups	55.04 ± 13.4 y.o							N/A
11-20						1	0.2	
21-30						13	3.0	
31-40						55	12.7	
41-50						86	19.9	
51-60						117	27.0	
61-70						110	25.4	
71-80						43	9.9	
81-90						7	1.6	
91-100						1	0.2	
Male	56.09 ± 13.57 y.o							
Female	53.75 ± 13.09 y.o							
Young patients	39.65 ± 6.87 y.o							
Old patients	62.71 ± 8.25 y.o							
Sex								0.659[a]
Male		77	53.5	161	55.7	238	55.0	
Female		67	46.5	128	44.3	195	45.0	
Male:Female	1.22:1							
Tumor locations								0.610[a]
Colon		69	47.9	146	50.5	215	49.7	
Rectal		75	52.1	143	49.5	218	50.3	
Side involvement								0.916[a]
Right		25	17.4	49	17.0	74	17.1	
Left		119	82.6	240	83.0	359	82.9	
Tumor subsites								0.189[a]*
Proximal large intestine		37	25.7	66	22.9	103	23.8	
Caecum		7	4.9	15	5.2	22	5.1	
Ascending colon		17	11.8	32	11.1	49	11.3	
Transverse colon		13	9.0	19	6.6	32	7.4	
Distal large intestine		107	74.3	223	77.2	330	76.2	
Descending colon		13	9.0	15	5.2	28	6.5	
Sigmoid		19	13.2	65	22.5	84	19.4	
Rectum		75	52.1	143	49.5	218	50.3	
Tumor size	5.97 ± 3.02 cm							0.559[a]
<5 cm		59	41.0	110	38.1	169	39.0	
≥ 5 cm		85	59.0	179	61.9	264	61.0	
Smallest size	1 cm							
Largest size	18 cm							
Metastasis								0.110[a]
M0		138	95.8	265	91.7	403	93.1	
M1		6	4.2	24	8.3	30	6.9	

[a]Chi-Square
*significant value for all tumor subsites

As described in **Table 2**., the appearance of most tumors shows exophytic lesions (83.1%), were of non-specific types (85.2%), are well-differentiated (67.7%), with pathological tumor staging pT3 (66.5%), have inadequate LN dissection (56.4%), with lymph node ratio staging LNR1 (57.5%), tumor stage IIA (34.2%), of an early stage (55.2%), with the absence of LVI (61.7%), and PNI (88.7%). Comparing the two groups, we found no differences in the proportion of clinicopathological and histopathological characteristics between young and old patients except in histological subtypes, adequacy of LN sampling, and PNI. Adenocarcinoma NOS is most prevalent in elderly patients, while the mucinous variant dominates in the young population ($p<0.05$). Older adults are more likely to get

inadequate LN dissection than young patients (p<0.01). A higher proportion of PNI was seen in the younger patients compared to elderly ones (p<0.001).

Table 2. Histopathological Characteristics of Tumor Between Young and Old Patients

Characteristics	Mean ± SD	Young (<50 y.o) (n=144)		Old (≥50 y.o) (n=289)		Total (n=403)		p-value
		n	%	n	%	n	%	
Growth pattern								0.413[a]
Exophytic		120	83.3	240	83	360	83.1	
Endophytic		15	10.4	21	7.3	36	8.3	
Ulcerative		8	5.6	22	7.6	30	6.9	
Linitis Plastica		1	0.7	6	2.1	7	1.6	
Histological subtypes								0.043[a]
Adenocarcinoma NOS		115	79.9	254	87.9	369	85.2	
Mucinous		19.4	19.4	35	12.1	63	14.5	
Signet-Ring Cell		0.7	0.7	0	0.0	1	0.2	
Tumor grade								0.591[b]
Well-differentiated		97	67.4	196	67.8	293	67.7	
Moderately differentiated		31	21.5	69	23.9	100	23.1	
Poorly differentiated		16	11.1	24	8.3	40	9.2	
Pathological tumor size								0.895[b]
pT1		3	2.1	8	2.8	11	2.5	
pT2		22	15.3	44	15.2	66	15.2	
pT3		94	65.3	194	67.1	288	66.5	
pT4		25	17.4	14.9	14.9	68	15.7	
Pathological node status								0.734[b]
pN0		80	55.6	168	58.1	248	57.3	
pN1a		18	12.5	42	14.5	60	13.9	
pN1b		18	12.5	34	11.8	52	12.0	
pN2a		18	12.5	33	11.4	51	11.8	
pN2b		10	10.0	12	4.2	22	5.1	
Adequacy of dissected node								
LN total positive	667							
LN total dissected	4,313							
Mean LN positive	1.54 ± 2.73							
Mean LN dissected	9.96 ± 5.46							
Inadequate (<12)		67	46.5	177	61.2	244	56.4	0.004[b]
Adequate (≥12)		77	53.5	112	38.8	189	43.6	
Lymph node ratio (LNR)	0.18 ± 0.29							0.967[b]
LNR1 (<0.05)		81	56.3	168	58.1	249	57.5	
LNR2 (0.05-0.20)		21	14.6	38	13.1	59	13.6	
LNR3 (0.20-0.40)		15	10.4	28	9.7	43	9.9	
LNR4 (≥0.40)		27	18.8	55	19.0	82	18.9	
Staging								0.431[b]
I		19	13.2	41	14.2	60	13.9	
IIA		48	33.3	100	34.6	148	34.2	
IIB		12	8.3	19	6.6	31	7.2	
IIIA		6	4.2	10	3.5	16	3.7	
IIIB		39	27.1	83	28.7	122	28.2	
IIIC		15	10.4	16	5.5	31	7.2	
IV		5	3.5	20	6.9	25	5.8	
Degree of Staging								0.921[a]
Early stage (I-II)		79	54.9	160	55.4	239	55.2	
Advanced stage (III-IV)		65	45.1	129	44.6	194	44.8	
Lymphovascular invasion								0.314[b]
Negative		84	58.3	183	63.3	267	61.7	
Positive		60	41.7	106	36.7	166	38.3	
Perineural invasion								0.000[b]

Negative	114	79.2	270	93.4	384	88.7
Positive	30	20.8	19	6.6	49	11.3

[a]Kruskal-Wallis; [b]Chi-Square; Percentage of total column; NOS, nonspecific

Figure 1 pictured histopathological findings of our CRC cases, and the descriptive proportions of them are presented in **Tables 1 and 2.**

<Figure 1>

This study employed an observational, analytic design with a cross-sectional method analyzing eleven years of data in a tertiary health care center. We analyzed the trend of CRC cases based on age and tumor sites in Indonesian patients. Furthermore, we generated a predictive model of CRC and compared clinicopathological and histopathological characteristics between young and old adult patients when diagnosed.

An analysis of CRC cases in **Figure 2** showed a significant ($p<0.05$) increase of annual percentage changes (APC) in the last eleven years in CRC for all patients, as well as all sub-populations (young and old patients) related to the anatomical location of the tumor (colon, rectum, and colon plus rectum). The CRC incidence also increased following the fit model of regression as demonstrated in **Figure 3,** and the subsequent five-year number cases can be predicted using specific predicted case equation formula.

< Figure 2>

<Figure 3>

Discussion

CRC incidence is considered a "new emerging public threat" as the incidence rates reach high proportions. Nevertheless, the epidemiology of CRC is not comprehensively discussed in the Indonesian population. Thus, the present study will holistically analyze an epidemiology-based pathology of 433 CRC cases recorded in Cipto Mangunkusumo Hospital, the national referral health center in Indonesia, between 2009 and 2019.

1. Clinicopathological and Histopathological Features Analysis of CRC

1.1. Tumor Subsites

A prospective multinational colonoscopy survey in Asia found that more patients had distal neoplasms than proximal neoplasm (45.2% vs. 39.3%).[18] This fact is corroborated in our result (distal vs. proximal tumor site = 76.2% vs. 24.8%). Interestingly, highlighting the proportion, there is a tendency of proximalization of colon cancer in young patients compared to old patients in our study (25.7% vs. 22.9%). This is not similar to findings of a Korean study, which found a higher proximal location in the older populations.[19] In the majority of patients, tumors occurred within the rectum. Rectal predominance was seen in both age groups, as previously mentioned in a study from India.[20]

1.2. Tumor Size

In this present study, two-thirds of patients are found with tumor size ≥ 5 cm, even with the largest size of 18 cm. Although some authors believe that tumor size does not affect prognosis, others believe that tumor size partially influences prognosis. [21,22] Increasing tumor size is associated with decreased loco-regional control resulting in the increased risk of its malignant potential.[23] Bigger tumors are more likely to be more profoundly invasive and invade neighboring organs. Rectal tumor size may also influence the risk of lateral pelvic nodal metastases in low rectal cancer.[24]

Local recurrence was significantly higher in patients having tumors measuring ≥5 cm in size, having poorly differentiated adenocarcinoma, having pathological T4 stage, and receiving adjuvant RT. Moreover, the 5-year overall survival rates in the patients having tumors measuring ≥5 cm in size (71.20%) were lower than in sizes < 5 cm (82.60%), respectively (log-rank, P = 0.001).[25]

1.3. Growth Pattern

Gross morphology varies, influenced by the growth phase at the time of diagnosis and the location in the large intestine. Small colorectal carcinomas grossly resemble adenomas in the early phase. In advanced carcinomas, the following growth patterns exist: Polypoid or exophytic with predominantly intraluminal growth, ulcerative or endophytic with predominantly intramural growth, and diffusely infiltrating (linitis plastica), which is characterized by a distinct desmoplastic reaction resulting in a rigid and thickened wall of the large intestine. Carcinomas can involve only part of or the whole circumference of the large intestine, resulting in annular or circular proliferation and causing constriction of the lumen.[15]

According to our findings, the proportion of growth patterns was (from highest to lowest) exophytic in both age groups, followed by endophytic, linitis plastica, and ulcerative. These findings agree with a previous study in Thailand, which found fungating and polyp mass (exophytic) was higher than ulcerative mass.[26] Our study demonstrated that a more common growth pattern is exophytic or polypoid (85.2%), higher in the elderly than young adults (87.9% vs. 79.9%). Ulcerative and linitis plastica were scarce in number, which is favorable since both growth modes entail a worse prognosis. The presence of an infiltrative growth pattern (linitis plastica) suggests de novo origin. De novo carcinogenesis, defined as the development of a tumor from normal (or intact) colonic mucosa, without the intervening step of an adenoma, has been a matter of discussion for decades, and has been associated with specific molecular characteristics, such as a reduced proportion of KRAS mutation.[27]

Clinically, de novo tumors may represent a more aggressive (quickly growing at an early stage) subtype of CRC. These results require more awareness and persistence in the colonoscopic detection of non-polypoid lesions (particularly in the proximal segment), more intensive surveillance of colonoscopically treated cases, and surgical treatment for selected patients. The tendency for worse behavior of non-polypoid lesions, as suggested by their increasing incidence with poorer disease progression and higher aggressiveness, may necessitate adequate readjustments in the diagnosis, treatment, and surveillance of these cases.[27]

1.4. Histological Subtypes

Most of the histological subtypes in our patients were adenocarcinoma NOS without mucin (85.2%), similar to the previous study 84%.[28] Our results showed that in younger patients, the proportion of adenocarcinoma NOS is lesser than older (79.9% vs. 87.9%, respectively) in agreement with a previous study by Chan et al. (84% vs. 92%, respectively)[28] and Gheju et al. (86.7% vs. 84.7%, respectively).[29] Mucinous histological variant was significantly higher in the younger than in the old (19.4% vs. 12.1%). Meanwhile, signet-ring cell was only observed in young patients.

Signet-ring cell carcinoma globally accounts for 0.6-1.0% of all CRC cases. Our patient who has signet-ring cell has these characteristics: only one lesion (0.4%): the average age of 48 years old, female sex, location in the caecum, right-sided, size 5.5 cm, brown color surface, exophytic, LNR 5/13 (adequate), pT3N2aM0 (IIIB), negative LVI, negative PNI, and a tumor grading of poor differentiation. In Romania, only patients with signet-ring cell carcinoma were found.[29]

Mucinous and signet-ring cell adenocarcinoma histological subtypes are generally considered poor prognostic factors. They also are more resistant to chemotherapy.[30] These subtypes were also more frequent in younger patients.[31]

Mucinous and signet-ring cell adenocarcinomas are associated with microsatellite instability (MSI), sporadic and hereditary nonpolyposis syndrome, and CRC with high degrees of methylation (CIMP).[32,33] The literature stated that mucinous histopathology was a significant predictor of poor outcome and more advanced node stage.[20]

Signet-ring cancers have intracellular mucin pushing the nucleus to one side and are associated with a more advanced stage at diagnosis, higher incidence of LVI, LNM, and liver metastases, as well as a higher rate of recurrence. It has been reported that it has different molecular pathways, which may explain its aggressiveness.[34,35]

Subsites analysis revealed that signet-ring morphology was significantly more prevalent in the caecum, similar to the previous study.[30] Mucinous adenocarcinoma is more often found in the ascending colon, and adenocarcinoma NOS has a higher proportion in the rectum. These findings were corroborated by Loree et al., who also reported characteristics of tumor grade that differed by tumor subsites and referred to distinct mechanisms of oncogenesis between LSCRC and RSCC.[36]

1.5. Tumor Grade

In both groups of age, most tumors were well-differentiated, similar to a previous study in India.[20] These results were different from a previous study by Chan et al.[28], which found that both age groups were mostly with cases of moderately differentiated tumor. In our study, poorly differentiated CRC was seen more frequently in younger patients (11.1% vs. 8.3%), highlighting the aggressiveness of tumor biology at a young age. In young patients with colorectal cancer, survival has been reported to be poorer compared with older patients.[37]

Some studies report poor prognosis in young adults diagnosed with CRC referred to poor differentiation along with signet-ring cell or mucinous adenocarcinoma in their histological subtypes.[38,39] However, despite significant results in histological subtypes, we found no significant difference in tumor grade in our patients.

1.6. Adequacy of Dissected Node

In our study, the average LN dissected was 9.96 ± 5.46, lower than in a previous study from Romania (35.7 LN removed), indicating that ideal sampling was complex in our institution.[29] The average number of positive LN per patient was 1.54 ± 2.73, which was lower than a previous study in Romania (3.7 (1-62)).[29] Thus, the interpretation becomes very complex because the number of LNs positive for tumor were lower in number, and there are more cases with inadequately removed LNs than in the Romanian study.[29] Thus, there is a high probability of LNs which have not been taken and could be positive for cancer spread. This will have a further impact on the staging of patients. It is well known that, although only 36-41% of hospitals are routinely meeting the recommended minimal sampling of 12 nodes, hospitals have improved their LN counts in these decades. Increasing the sampled LN leads to increased accuracy in node status and determination of the appropriate therapy for patients.[40] Moreover,

in a recent Dutch nationwide study,[41] the authors found that with an increasing number of evaluated nodes, the risk of death is decreased, related to a better quality of surgical resection (yielding more LN for the pathologist to assess).

The average number of LN dissected is inadequate in this study, and there are significant differences between the two age groups. In the younger patients, the adequacy number is higher than in the older population, showing a favorable finding in our young patients in Indonesia. In the present study, elderly patients are more likely to receive inadequate lymph node dissection during operative therapy ($p<0.001$), similar to a previous study due to elderly patients being at a higher surgical risk for various postoperative complications along with their comorbid diseases, possibly making surgeons considering the risks and benefits of a more thorough LN dissection.[42]

The number of LN dissected from resection specimens depends on several factors, including the surgeon's technique, bowel resection length, and tumor location. We observed the factors of tumor location. We found that ascending colon became the location with the highest number of LNs taken reflected that it is the most accessible area to remove LN. This is followed by the descending colon, transverse colon, caecum, sigmoid, and rectum. The rectum seems to be an area with the most difficulty removing all LN. These findings also have been observed in a previous study.[43]

The literature asserted that more LN is usually obtained from RSCC than LSCRC, and the lowest number is from rectal cancers.[44] The reasons for this difference are still not fully understood. Anatomical reasons indicate that more numerous intermediate nodes can be found in and around the ileocecal region than in the mid-, left, and sigmoid colon. This may partially explain higher LN yield in right-sided hemicolectomy specimens than in left-sided colon resection specimens. In addition, difficulties in LN dissected from rectal resection specimens are addressed by Cawthorn et al.[45], who found that LNM in the supra-levator part of the mesorectum may be challenging to identify by manual dissection.

1.7. Lymph Node Ratio

The scientific evidence for a minimum LN number of 12 is questionable, and the use of a more reasonable and practical LN number should be determined based on LNR, which is a ratio of the numbers of positive LN per dissected LN. However, it remains unclear how we should categorize patients based on the LNR, and future prospective studies are needed to define the cut-off values that allow for optimal separation between subgroups. In our patient, the best match for our LNR grouping is using four groups and cut-off values as such: <0.05 (LNR1), 0.05-0.20 (LNR2), 0.20-0.40 (LNR3), and 0.40-1.00 (LNR4).

Our average LNR in this study was 18 ± 2.9% lower than a previous study in Romania (22.1% (1.39-100%)),[29] consistent with our adequacy results, which were more inadequate but with less positive LN possibly resulting in a lower class for LNR.

LNR provides stronger and superior prognostic power than the number of positive nodes alone. A meta-analysis confirmed that higher LNR is statistically significantly associated with poor survival of CRC.[46] It is recommended to include LNR as a prognostic parameter in future colorectal staging systems. It is important to note that the extent of dissection would influence the LNR.

1.8. Lymphovascular Invasion

Another adverse impacting prognostic feature, lymphovascular invasion (LVI), was detected less frequently in our study (38.3%) compared to a previous report by Elsamany et al.[47] However, the proportion of positive LVI was higher in the young population compared to the elderly (41.7% vs. 36.7%). These findings indicate that LVI is an important histopathological feature to assess in young patients.

1.9. Perineural Invasion

We found a tiny proportion of positive perineural invasion (PNI) in all patients (11.3%) than in the study Elsamany et al.[47] (24.4%). However, we found a higher proportion of PNI in the young population (20.8%) than the elderly (6.6%), similar to a study by Zahir et al.[48] showing that 22% of young patients with CRC had positive PNI.

The presence of perineural invasion is associated with a higher rate of metastatic disease, recurrence, and reduced survival. Several studies have increasingly recognized it as a notable independent prognostic factor in the CRC multivariate analysis.[49]

2. Trend Analysis of CRC

In this present study, the colorectal, colon, and rectal cancer APC for all patients were +11.81%, +10.80%, and 13.58%, respectively. When compared with the WHO prediction for Indonesia, the increase of colorectal cancer was tremendous and will be higher than in the current period, +17.7% overall, +18.1% of colon cancer and +17.3% of rectal cancer in both sex during 2020-2025.[50] The trend of CRC in Indonesian patients has not been demonstrated previously. Our trend results were higher than the previous study for early-onset CRC incidence rates, which increased from 1998 to 2007 in Arizona.[51] Due to scarce documentation, we only obtained sporadic studies about CRC in Indonesia. In South Sulawesi,[52] 466 cases of CRC were observed in the period 2013-2015; in Jakarta[53] 317 colon cancer and 504 rectal cancer cases were reported from a single center between 2008-2012; in South Sumatera[54] 105 cases were described during 2013-2016; in Bali[55] 275 samples were found in 2014-2016 with a young population percentage of 31.3%, similar to our study. In the last few decades, the incidence of colorectal cancer has been increasing in Asia and many ASEAN countries, including Indonesia and Malaysia.[56] If this trend continues, the number of CRC cases may suddenly overwhelm the health care system. Thus, better health policy should be constructed by the government.

Moreover, we use an interesting technique to predict CRC trends by doing fit-model regression to predict colon and rectal cancer incidences. Overall, colon cancer cases fitted a quadratic prediction model, and the rectum had an S-shaped prediction model. In young adults, the colon cancer cases fitted a J-shaped prediction model; meanwhile, rectal cancer cases were predicted to have an S-curve. In the elderly, both colon and rectal cancer cases showed a quadratic model with a decreasing trend for rectal cancer.

2.1. Case Analysis Based on Age Groups

The majority of CRC in other studies was diagnosed in the middle-aged and elderly population around 55 years,[37] similar to our study (55.04±13.4 y.o); the female age of majority was younger than the male, similar to a previous study conducted in Brunei Darussalam (59.3±14.6 y.o, female also younger than male).[57] The definition of "early-onset" CRC is arbitrary in the literature; we selected 50 years as the cut-off age due to this recommended time point for initial screening in most screening programs, which progressively entered use globally.[10] Early-onset CRC is more likely to occur sporadically in third world countries, rarer in a developed country, and hypothetically is a biologically and clinically distinct entity, accounting for its aggressive presentation and poorer survival.[48,58,59] We report an incidence of early-onset CRC of 144 out of 433 (33.26%) at our institution during the study period, which is substantially higher than what data in Western countries suggests. This is also higher than estimates from other Asian studies,[28,60] although comparable to India's.[58] The highest incidences of early-onset CRC may be in South

Asia, ranging from 38% to 52%.[20,58] This fact is due to their significant and increasing young population as a demographic bonus similar to what is being experienced by the Indonesian population.

The cause of increasing incidence in young-onset CRC in Indonesia and Asia has yet to be fully elucidated. We believe that early-onset CRC is multifactorial, and genetic mutations along with lifestyle changes are likely contributory.[51] Molecular profiles of Indonesians are found to progress in distinct pathways.[8] Our young Indonesian cases, mainly found in distal locations for CRC, are not in line with characteristics for hereditary CRC, primarily found in proximal sites. They also did not follow the conventional pathways of sporadic CRC (the CIN pathway). Instead, it is mixed with MSI and inflammatory pathways, including cyclooxygenase-2 (COX-2) and nucleus factor κB (NF-κB). Also, lower mutation rates of the pro-oncogene KRAS are found among young Indonesian patients.[8] Sudoyo et al. studied five hospital-based reports (121 cases) in 2010 and obtained 56.5% of CRC cases positively staining for MSH2, and 16.5% positively staining for MLH1.[61] Another point of histopathological characteristic is that signet-ring cell carcinoma - an aggressive subtype of CRC that spreads rapidly and is characterized by late symptom manifestations - disproportionately affects young individuals.[62] A genome-wide association analysis study for multiethnic Indonesians by Yusuf et al. characterized the relationship between variants in the *SCL22A3, SCG5, GREM1*, and *STXBP5-AS1* genes for colorectal cancer in the diverse Indonesian population.[63] Thus, it is conceivable that intrinsic immunologic differences between young and old patients also interacts with age-related immunosenescence, T-cell dysregulation, and systemic inflammation.[64]

Moreover, complex epigenetic interactions due to emerging environmental and lifestyle risk factors are also related to these CRC cases. Early life encompasses periods of increased susceptibility to the deleterious effects of several risk factors due to their high cell division and turnover rates. Those factors are: **(1) Smoking**: a modifiable risk factor responsible for 8.4% of CRC incidence.[57] Smoking early in life may also play a part in the high incidence observed in young Indonesian people due to the frequency of daily smoking in young adults: 24.3% (95%CI: 24.1-24.4%).[65] Smoking is associated with hypermethylation, microsatellite instability, and BRAF mutations in CRC carcinogenesis.[66] **(2)** The risk of CRC was also increased by **alcohol** consumption. It has been reported that both frequent and high amounts of alcohol consumption had positive associations with the risk of distal colon cancer in Korea.[67] A study from Japan indicated that alcohol consumption in males demonstrated a dose-response relationship with the risk of cancer in the distal colon and rectum but not in the proximal colon.[68] In Indonesia, the proportion of alcohol consumption in the Indonesian population aged more than ten years for males is 6.1% (95%CI: 6.0-6.2%), much higher than females: 0.4 (95%CI: 0.4-0.5%).[65] **(3)** A recent study of Asian also observed that **obesity** has a positive association with risk of colon cancer but not risk of rectal cancer in women and men.[57] This study reflected the condition in Indonesia, which obesity also showed high prevalence in the population over 18 years. Obesity is more prevalent in the women population: 29.3% (95CI: 29.1-29.6%) compared to men: 14.5% (95CI: 14.3-14.7%).[69] Obesity can promote cancer formation through metabolic abnormalities, hyperinsulinemia, systemic inflammation, and alteration of the gut microbiota.[70] **(4)** CRC increase in Indonesia also probably due to the acquisition of the **Western lifestyle,** referring to a dietary composition with more red and processed meat and less fruit and vegetable.[71] This lifestyle trend has been seen in Indonesian teenagers who consume inadequate amounts of protein, fruits, vegetables, and excessive amounts of sodium and fast food.[72] **(5)** Increasing obesity is approximately concurrent with **reductions in physical activity** levels.[73] A systematic review in Japanese found an inverse association between physical activity and CRC, and this association was stronger for colon than rectal cancer.[74] This fact agrees with a survey in Indonesia that found that 33.5%

(95%CI: 33.3-33.8%) of the Indonesian population aged ten years and above lacked physical activity according to time, frequency, and MET standards.[65] **(6)** Another related risk factor is **early-life antibiotic use**. This risk factor is present in Indonesia's population, including high exposure to antibiotics during their lifetime. Due to frequent misuse, Indonesia is now a country with a high level of antibiotic resistance.[75] These early-life antibiotic exposures could disrupt the gut microbiota, alter the metabolic profile and lead to a higher risk of obesity in later life.[76]

Other potential explanations for the rising trends among Indonesia's young population are an unavoidable risk of several biases. This study would ensure more significant concern and provide better facilities for cancer detection than those available generally in the country. This may result in inflation of the prevalence results derived. In our home country, a CRC screening program has not been established well before the national health insurance era (before 2014), and recently it has improved.[77]

The impact of age is crucial due to their prognosis. The prognostic outcomes of young populations are inconsistent;[44] results suggest worse survival outcomes,[31,38] whereas others suggest equal prognosis between the two groups or better prognosis depending on staging reported (early or advanced).[37,78] Notably, more aggressive treatment to young patients has consistently been documented in the literature to result in improvements in general survival.[73]

2.2. Case Analysis Based on Tumor Locations

Overall, in this present study, 49.7% of the patients had colon cancer, while the rest had presented with a diagnosis of rectal carcinoma. We found that rectal cancer tends to be more common in the young population (52%) compared to the elderly (49.5%). Equal prevalence of colon and rectal cancer in this study is also seen in countries that have historically "low risk" of CRC.[59,79]

The rectum becoming the most common site followed by the sigmoid colon is consistent with a previous study conducted in Saudi Arabia.[80] It should be noted that the increase in rectal cancer, especially in younger populations, may imply additional factors behind these changes. Certain lifestyle factors relevant to the young population have site-specific effects on colorectal carcinogeneses, such as processed meat consumption with rectal tumors compared to the most common etiology of the more proximal part of the colon caused by hereditary causes.[81]

Conclusions

Young-onset colorectal cancer was discovered with a worryingly rising incidence. It was characterized by early-stage and well-differentiated tumor at presentation, left-sided involvement, and several distinct histopathological features highlighted in young patients for predicting poor disease outcomes (i.e., LVI and LNR). Policies regarding particular screening protocols, educational activities, and lifestyle modifications customized to the Indonesian health infrastructure are urgently needed to deal with this challenging situation.

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Patient consent for publication

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Ethics approval

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Data availability statement

All data relevant to the study are included in the article.

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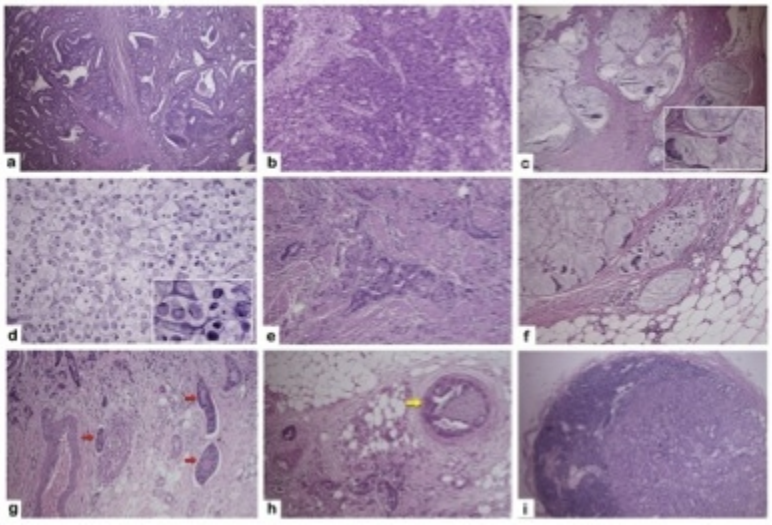
Figure Legends

Figure 1. Histopathological features of colorectal cancer resection specimen (all in HE staining). (a) well-differentiated adenocarcinoma NOS (M40x); (b) poorly differentiated adenocarcinoma NOS (M40x); (c) mucinous adenocarcinoma (M40x, inlet 100x); (d) signet-ring cell carcinoma (M40x, inlet 400x); (e) pT2 stage tumor infiltrating muscular layer (M40x); (f) pT3 stage tumor infiltrating adipose tissue in sub-serousal layer (M40x); (g) lymphovascular invasion (pointed by red arrow, M40x); (h) perineural invasion (highlighted by yellow arrow, M40x); (i) lymph node metastasis (M100x)

Figure 2. Time trend of colorectal cancer incidence among 433 patients counted by anatomical subsites. Colon plus rectum indicated a total incidence of both locations. Plotted lines indicate annual percentage changes (APCs). *Significant change in APC versus 0 ($p<0.05$) using the permutation model of logarithmically transformed data in Joinpoint regression analysis.

Figure 3. Annual incidence trends, the equation for predicting cases, and forecast number of cases in the next-five year using fit-model regression analysis model for colorectal cancer in all, young, and old patients counted by anatomical subsites. *Indicates significantly progression slope ($p<0.05$; ANOVA statistical test); Connected points show actual rates, and the fit-model regression line is shown as a straight line.



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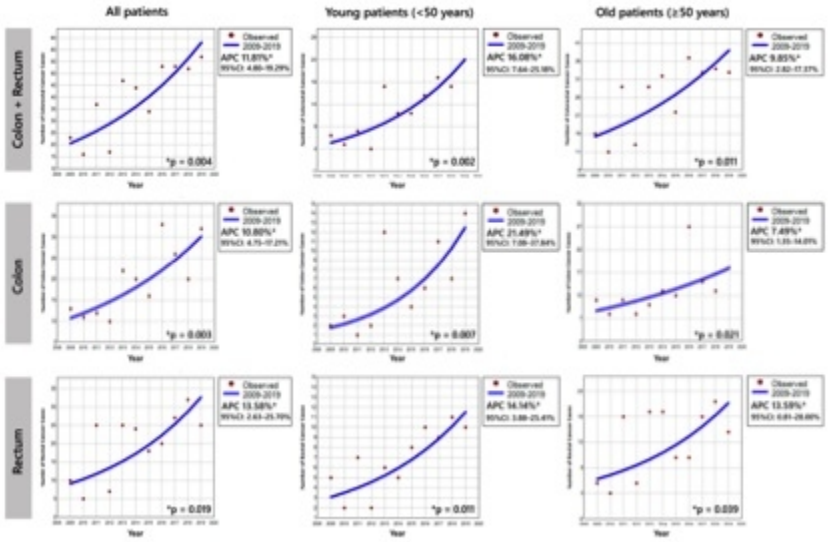

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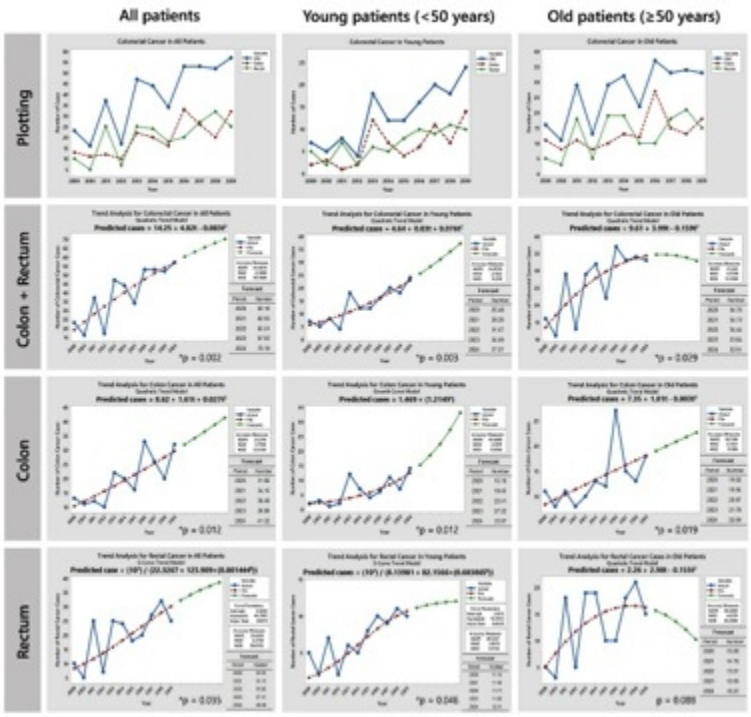
147x96mm (72 x 72 DPI)



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S1 File. STROBE Checklist 2007 (v4) Statement—
Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	2-3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-3
Bias	9	Describe any efforts to address potential sources of bias	2
Study size	10	Explain how the study size was arrived at	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	2-3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	3
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	3
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4
		(b) Indicate number of participants with missing data for each variable of interest	N/A
Outcome data	15*	Report numbers of outcome events or summary measures	3-5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4-6
		(*b*) Report category boundaries when continuous variables were categorized	3-6
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a	N/A

		meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N/A
Discussion			
Key results	18	Summarise key results with reference to study objectives	6-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	6-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Forecasting Colorectal Cancer Trends in Young Patients: Eleven Years of Experience at the Indonesian National Referral Hospital

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Forecasting Colorectal Cancer Trends in Young Patients: Eleven Years of Experience at the Indonesian National Referral Hospital

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Running Title: Trends of Colorectal Cancer in Indonesian Patients

Abstract

Objective: To obtain annual incidence trends, understand clinicopathological characteristics, and forecast the future burden of colorectal cancer (CRC) in Indonesia.
Design: An 11-year retrospective study.
Setting: A main national referral hospital in Jakarta, Indonesia.
Participants: 1,584 eligible cases were extrapolated for trend and forecasting analysis; 433 data were analyzed to determine unique clinicopathological characteristics between young (<50 years) and old (≥50 years) patients.
Methods: Trend analyses were done using Joinpoint software, expressed in annual percentage change (APC), and the regression analysis was executed to generate a forecasting model. Patients' characteristic data were calculated using chi-square or nonparametric tests.
Main outcomes: Analysis of trend, forecasting, and clinicopathological features between two age groups.
Results: For CRC cases, a significant increased APC was observed among old patients (+2.38%). Colon cancer increased most remarkably (+9.24%) among young patients; meanwhile, rectal cancer trends were stable and declining. The trend for right-sided CRC increased in the general population (+6.52%) and old patients (+6.57%), while the trend for left-sided CRC was stable. The majority of cases are expected to be a significant future burden within the next ten years. Patients had a mean age of 53.17±13.94, and 38.1% were young, with a sex ratio of 1.21. Prominent characteristics were left-sided CRC, tumor size ≥5 cm, exophytic growth, adenocarcinoma, histologically low-grade, pT3, pN0, inadequately dissected lymph nodes (LN), LN ratio (LNR) <0.05, no distant metastasis, early stage of cancer, no lymphovascular invasion (LVI), and no perineural invasion (PNI). Distinct features between young and old patients were found in the subtypes, histological, dissected LN number, and PNI of tumors.
Conclusions: Epidemiological trends and forecasting of CRC cases in Indonesian patients showed an enormous increase, notably for colon cancer, with a particularly concerning trend in young patients. Additionally, young patients exhibited particular clinicopathological characteristics that contributed to the disease's severity.
Keywords: clinicopathological characteristics, colorectal cancer, histopathological characteristics, Indonesia, retrospective analysis, young patients, trend analysis.

Strengths and limitations of this study

- We offer the first epidemiological report on incidence rates of colorectal cancer (CRC) cases based on tumor locations and side involvement, as well as clinicopathological characterization from a retrospective cross-sectional analysis of Indonesian patients with ample long coverage time (2009 to 2019).

- We provide trend analysis to determine changes in the annual incidence of CRC in Indonesia based on age, tumor locations, and side involvement of cancer, along with developing a CRC forecasting model to estimate case patterns over the next ten years.
- This study draws an association between highlighted incidence among young patients and feasible explanations based on recognized clinical and histological features in order to help create future interventions.
- This research was limited by the data originating from a single-center, the inherent record bias of the retrospective study design, and the exclusion of samples due to data loss from medical record retention and deterioration of slide staining.
- This research was also limited because associated data related to risk factors was not recorded, such as family history, hereditary cancer syndromes, socioeconomic characteristics, and the basis of diagnostic test frequency, which could explain the trend.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer globally, and it is becoming more common, especially in developing countries.[1] CRC is usually diagnosed through endoscopic biopsy or polypectomy. Microscopic examination is used to search for invasions. In the new era of personalized medicine, the role of anatomical pathologists has been dramatically expanded. Their role is no longer limited to providing histopathologic diagnosis but also assessing staging, margins, and prognostic parameters that can only be made available by microscopic examinations such as tumor grade, lymphovascular invasion (LVI), and perineural invasion (PNI). Further research about the pathological characteristics of CRC is essential for treatment approaches and policymaking.

Recent long-term studies discovered that young people under 50 years old are more likely to get colon cancer, especially in high-income countries.[2,3] These studies showed the changing CRC epidemiology in clinical, histopathological, prognosis, and treatment.[4] By 2030, more than 1 in 10 colon cancer and nearly 1 in 4 rectal cancer cases are projected to be diagnosed in this age group for whom routine screening is currently not recommended.[5] This phenomenon is presumably due to rapid changes in lifestyle and diet and genetic alterations in high-risk populations. A study in the US found that cancer in young patients rose by 17%. Similar trends have been seen in several Asian countries, including China, Japan, India, and South Korea, where a huge rise in the number of young patients with CRC has been documented.[2,6]

A better epidemiological perspective of CRC from other parts of Asia, including Southeast Asia, is needed since cases are relatively less researched and are becoming a current public health threat. Furthermore, in the population younger than 50 years old, CRC shows a rising incidence and appears to display a more aggressive phenotype with unique genetic profiles, critical differences in somatic gene mutations, and gene methylation.[7] Distinct molecular carcinogeneses and genomic profiles of CRC in Indonesia drive us to give a broader view of CRC in terms of epidemiology and clinicopathological characteristics,[8–10] for which no previous thorough investigation of these topics has been published in Indonesia. These knowledge gaps support us in researching how the colon, rectal, and colorectal cancers changed in 2009–2019 for young patients under 50 years old compared to their older counterparts. We also aimed to obtain annual incidence trends, understand clinicopathological characteristics, and forecast the future burden of CRC in Indonesia.

Materials and Methods

Study Design, Ethical Clearance, Data Collection, and Selection Process

This retrospective cross-sectional study was conducted at the Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, to analyze CRC incidence from 2009 to 2019 using pathology archives and hospital medical records. Ethical approval (KET-139/UN2.F1/ETIK/PPM.00.02/2020, protocol number: 10-11-

1416) was obtained from the Institutional Ethical Review Board (IERB) of the Faculty of Medicine, Universitas Indonesia. General consent for the use of medical record data and residual material had already been obtained, in line with ethical approval.[11–13] Data from 2020 was not included to avoid bias due to the COVID-19 pandemic impact, which decreased the volume of CRC patients arriving at the hospital. In total, 1,958 patients have had a malignant tumor in the colon or rectum based on ICD-O topography (C18-C20) and morphology (M8140/3, M8480/3, and M8490/3) codes, and with adequate biopsy or resection specimens to be enrolled in this study.[14] For the analysis of trends, forecasting, and clinical data, 1,584 patients were selected by exclusion criteria (i.e., duplication of inputted cases and changing diagnosis or metastasis), and 433 resection samples with complete data were assessed in the final for pathological characteristics analysis between two age groups, as shown in **Figure 1.**

<**Figure 1.>**

Extraction and Definition of Variables

The variable of age, registration year, sex, tumor location, site of colon cancer, side involvement of CRC, and specimen type were extracted directly from cancer registry data. Tumor size, growth pattern, histological subtypes, and metastasis characteristics were retrieved from hospital medical records and pathological reports of patients who underwent surgery.

The young patient population was defined as subjects under 50 years, agreeing with previous studies.[15] Pathology specimens for each patient were examined under the microscope by two independent pathologists who recorded the histopathology characteristics of pathological tumor staging, histological subtypes, growth pattern, tumor grade, LVI, and PNI. We evaluated the number of dissected lymph nodes (LNs) in agreement with other studies and WHO guidelines, with a minimum of 12 LNs taken for each case.[16–18] Along with LNs, we also calculated the lymph node ratio (LNR) as the number of positive LNs divided by the number of LNs examined. This parameter was introduced as a significant predictor of survival in other malignancies and could be classified into subgroups according to the following cutoffs: <0.05 (LNR1), 0.05–0.20 (LNR2), 0.20–0.40 (LNR3), and 0.40–1.00 (LNR4).[19]

The tumor site was defined as the location where the primary tumor originated. Right-sided CRC (RSCRC) originates from the caecum, ascending colon, hepatic flexure, and transverse colon. Left-sided CRC (LSCRC) originates from the spleen flexure, descending colon, sigmoid colon, and rectum.[20] Proximal colon cancer originated from the caecum, ascending, and transverse colon. Meanwhile, distal colon cancer occurs in the descending colon and sigmoid colon.[14,21] Tumor size was the largest dimension of the three-dimensional tumors, classified into two: <5 cm and ≥5 cm. Metastasis was defined as distant metastasis confirmed by radiography or pathology diagnostic procedure. Pathological staging was based on the World Health Organization (WHO) guideline and American Joint Committee on Cancer (AJCC) 8th Edition.[17,18] Based on subtypes, a tumor can be classified as adenocarcinoma not otherwise specified (NOS), mucinous adenocarcinoma, and signet-ring cell carcinoma variant. Advanced stage tumors are tumors with pT3-T4-stage or pTNM staging III-IV. The tumor growth pattern was classified into exophytic, endophytic, ulcerative, and linitis plastica.[22] Tumor grade was classified as well-differentiated, moderately differentiated, and poorly differentiated, according to a WHO classification based on the percentage of gland formation in the tumor mass.[17] LVI and PNI were defined as the occurrence of each parameter in at least one slide of the pathology specimen sample.[23]

Statistical Analysis and Presentation of Data

We performed a sub-analysis for each outcome measure during the sampling process (**Figure 1**) to address the missing data. A comprehensive data set from biopsy and resection specimens were utilized to extrapolate the CRC trend over eleven years and conduct a comparative analysis for a registered year, age, sex, tumor location, proximalization of colon site, side involvement, and tumor subsites, and specimen. To conduct a more detailed analysis of pathology data, we used only resection specimens. All missing data came from the retention of medical records and slide deterioration, hampering the reassessment process.

Data were then recorded and processed using the Statistical Package for Social Sciences (SPSS) v.25.0 statistical software with Chi-Square and its alternative tests (Fisher's exact, Kruskal-Wallis, or Mann-Whitney tests). Analysis was performed for the young and old patient populations for clinicopathological characteristics. The mean value of quantitative parameters (number of positive and dissected LNs, LNR, and tumor size) was compared between two groups of age with the t-student test. Annual incidence rates were quantified using Joinpoint regression (version 4.9.1.0; US National Cancer Institute Surveillance Research Program) which automatically joined separated time series on a logarithmic scale, expressed as the annual percentage change (APC).[24] Its significance of trends was assessed by a Monte Carlo permutation test.[25] We also performed a mathematical function as a linear and non-linear regression analysis to construct the best-fitted model to forecast the increased trend of CRC cases in the next ten years (2020–2029) using Minitab® 19.1 (64-bit).[26–32] The model trend equation to predict CRC cases can be visualized in linear [$Y_t = b_0 + (b_1 * t)$], quadratic [$Yt = b_0 + b_1 * t + (b_2 * t^2)$], exponential growth [$Y_t = b_0 + (b_1^t)$], or S-curve (Pearl-Reed logistic) [$Y_t = (10^a) / (b_0 + b_1 * b_2 t)$] with the letters represent the following: Y_t being the variable, b_0 being a constant, b_1 and b_2 being coefficients, and t as the value of the time unit. The best-fitted model is the model which has the lower values for three parameters (MAPE, mean absolute percent error; MAD, mean absolute deviation; and MSD, mean square deviation), or at least for two parameters or having the lowest value for MAPE.[30,33,34] The MAPE expresses accuracy as a percentage of the error. The MAD expresses accuracy in the same units as the data, which helps conceptualize the amount of error. The MSD measures the accuracy of the fitted time series values. After deciding on the model, we measured their significance slope using the ANOVA test for curve estimation in SPSS. Statistical analyses with a p-value <0.05 and a 95% confidence interval (CI) for probability were significant.

Patient and Public Involvement Statement

It was not possible to involve patients or the public in our research's design, conduct, reporting, or dissemination plans. This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (including cross-sectional studies), as stated in **Research Checklist**.[35]

Results

Of the 1,584 people diagnosed with CRC in this study, males dominated the CRC cases registered in our center, with the ratio of sex (male: female) being 1.21. Distribution based on age groups, as shown in **Table 1,** demonstrated that the highest proportion of CRC was found in ages 51–60 y.o.; the mean age was 53.17 ± 13.94 y.o., with females (52.28 ± 13.98 y.o.) generally being younger than males (53.90 ± 13.89 y.o.), p=0.021. Looking at the more specific age groupings, we found that the number and proportion of our patients' age was: 11–20 (11; 0.7%), 21–30 (81; 5.8%), 31–40 (225; 14.2%), 41–50 (339; 21.4%), 51–60 (432; 27.3%), 61–70 (334; 21.2%), 71–80 (135; 8.5%), 81–90 (20; 1.3%), and ≥91 (7; 0.4%). The

mean age of the young patient population was surprisingly very young (38.82 ± 7.46 y.o.). The proportion of young patients in this center reached 38.10% (n = 604) of the total incidence (n = 1,584). Rectal cancer now accounts for the biggest proportion of colon equivalents in our center (64.3% vs. 35.7%), proximal and distal colons were similar in number (49.6% vs. 50.4%), and the left-sided CRC was still the highest in proportion (82.3%). The sigmoid colon is the most often affected area in colon cancer.

Table 1. Clinicopathological characteristics of tumors between young and old patients (n = 1,584)

Characteristics	Young patients (<50 y.o.) (n=604)		Old patients (≥50 y.o.) (n=980)		All patients (n=1,584)		p-value
	n	%	n	%	N	%	
Registered-year case							0.931[a]
2009	49	8.1	70	7.1	119	7.5	
2010	52	8.6	94	9.6	146	9.2	
2011	47	7.8	83	8.5	130	8.2	
2012	52	8.6	76	7.8	128	8.1	
2013	50	8.3	89	9.1	139	8.8	
2014	69	11.4	103	10.5	172	10.9	
2015	64	10.6	91	9.3	155	9.8	
2016	48	7.9	81	8.3	129	8.1	
2017	47	7.8	91	9.3	138	8.7	
2018	54	8.9	96	9.8	150	9.5	
2019	72	11.9	106	10.8	178	11.2	
Sex							0.056[a]
Male	313	51.8	556	56.7	869	54.9	
Female	291	48.2	424	43.3	715	45.1	
Tumor locations							**0.002[a]**
Colon	187	31.0	379	38.7	566	35.7	
Rectal	417	69.0	601	61.3	1,018	64.3	
Proximalization of colon							0.572[a]
Proximal colon	96	51.3	185	48.8	281	49.6	
Distal colon	91	48.7	194	51.2	285	50.4	
Side involvement							0.131[a]
RSCRC	96	15.9	185	18.9	281	17.7	
LSCRC	508	84.1	795	81.1	1,303	82.3	
Tumor subsites							**0.002[a]**
Caecum	20	3.3	58	5.9	78	4.9	
Ascending colon	52	8.6	75	7.7	127	8.0	
Transverse colon	24	4.0	52	5.3	76	4.8	
Descending colon	33	5.5	46	4.7	79	5.0	
Sigmoid	58	9.6	148	15.1	206	13.0	
Rectum	417	69.0	601	61.3	1,018	64.3	
Specimen							0.135[a]
Biopsy	267	44.2	471	48.1	748	46.6	
Resection	337	55.8	509	51.9	846	53.4	

[a]Independent samples t-test [a]Chi-Square test; *Significant value for all tumor subsites

A trend analysis of CRC cases in Indonesian patients, as illustrated in **Figure 2,** showed an APC in the last eleven years for all patients, as well as all sub-populations (young and old patients), related to the anatomical location of the tumor (colon, rectum, or colon plus rectum) and side involvement of CRC (right-side vs. left-side). A significant APC was observed among all patients in the annual incidence of

colon cancer (+6.38%) and RSCRC (+6.52%). Looking more specifically at young patients, we identified significant APC only in colon cancer (+9.24%); meanwhile, in old patients, significant APC can be seen in CRC as a whole (+2.38%), colon cancer (+5.11%), and RSCRC (+6.57%). Trends were positive for all CRC sites, except the rectum, which tended to be stable in old patients (+0.58%) and decrease among the general population (–0.09%) and young patients (–0.97%) with p>0.05. More detailed data about the trend analysis of our CRC patients were recorded in **Supplementary Files 1-3**.

<**Figure 2.**>

We also investigated the increase of colon cancer based on their subsites (caecum, ascending colon, transverse colon, descending colon, and sigmoid colon) as visualized in **Figure 3**. The significant positive APC value was observed highest in ascending colon (+10.60%), followed by descending (+10.04%), transverse (+9.88%), and sigmoid colon (+5.84%).

<**Figure 3.**>

Furthermore, we generated a predictive model of CRC using a best-fitted regression analysis model, as demonstrated in **Figure 4.** The subsequent ten-year annual incidence rates for CRC cases can be predicted using a specific case equation formula obtained from regression analysis. The assumption of linearity in cancer incidence trends over the eleven years for our institutional cancer registry data was evaluated using the p-value for the slope in linear regression models. The p-value from the ANOVA test for curve estimation of the slope was reported for each regression. The precise number of predicted cases for the next ten years (2020–2029) can be read in **Supplementary Files 4-6** and **Supplementary Table 1**. The average future burden CRC from 2020 to 2029 compared to the current 11-year data in all, young and old patients (**Table 2)** was ~180 cases/year (vs. 144 cases/year), ~67 cases/year (vs. 55 cases/year), and ~112 cases/year (vs. 89 cases/year) respectively.

<**Figure 4.**>

As described in **Table 2**, most tumor sizes were equal to or more than 5 cm (61%), with a predominance of brown color. Assessing distant metastasis, around 4.2% of the cases developed metastasis. The appearance of most tumors shows exophytic lesions (83.1%), were of nonspecific types (85.2%), are well-differentiated (67.7%), with pathological tumor staging pT3 (66.5%), most cases having inadequate LN dissection (56.4%), lymph node ratio staging LNR1 (57.5%), tumor stage IIA (34.2%), of an early stage (55.2%), with the absence of LVI (61.7%), and PNI (88.7%). Comparing the two groups, we found no differences in the proportion of clinicopathological and histopathological characteristics between young and old patients except in histological subtypes, adequacy of LN sampling, and PNI. Adenocarcinoma NOS is most prevalent in old patients, while the mucinous variant dominates in young patients (p<0.05). Old patients are more likely to get inadequate LN dissection than young patients (p<0.01). A higher proportion of PNI was seen in the young patients than in their older counterparts (p<0.001).

Table 2. Pathological characteristics of tumor between young and old patients who underwent surgical resection with complete data (n=433)

Characteristics	Young patients (<50 y.o.) (n=144)		Old patients (≥50 y.o.) (n=289)		All patients (n=403)		p-value
	n	%	n	%	n	%	
Tumor size							0.559[a]
<5 cm	59	41.0	110	38.1	169	39.0	
≥ 5 cm	85	59.0	179	61.9	264	61.0	
Growth pattern							0.814[b]
Exophytic	120	83.3	240	83	360	83.1	
Endophytic	15	10.4	21	7.3	36	8.3	
Ulcerative	8	5.6	22	7.6	30	6.9	
Linitis Plastica	1	0.7	6	2.1	7	1.6	
Histological subtypes							**0.025[b]**
Adenocarcinoma NOS	115	79.9	254	87.9	369	85.2	
Mucinous	19.4	19.4	35	12.1	63	14.5	
Signet-Ring Cell	0.7	0.7	0	0.0	1	0.2	
Tumor grade							0.591[a]
Well-differentiated	97	67.4	196	67.8	293	67.7	
Moderately differentiated	31	21.5	69	23.9	100	23.1	
Poorly differentiated	16	11.1	24	8.3	40	9.2	
Pathological tumor size							0.587[b]
pT1	3	2.1	8	2.8	11	2.5	
pT2	22	15.3	44	15.2	66	15.2	
pT3	94	65.3	194	67.1	288	66.5	
pT4	25	17.4	14.9	14.9	68	15.7	
Pathological node status							0.734[a]
pN0	80	55.6	168	58.1	248	57.3	
pN1a	18	12.5	42	14.5	60	13.9	
pN1b	18	12.5	34	11.8	52	12.0	
pN2a	18	12.5	33	11.4	51	11.8	
pN2b	10	10.0	12	4.2	22	5.1	
Adequacy of dissected node							
Inadequate (<12)	67	46.5	177	61.2	244	56.4	**0.004[a]**
Adequate (≥12)	77	53.5	112	38.8	189	43.6	
Lymph node ratio (LNR)							0.967[a]
LNR1 (<0.05)	81	56.3	168	58.1	249	57.5	
LNR2 (0.05-0.20)	21	14.6	38	13.1	59	13.6	
LNR3 (0.20-0.40)	15	10.4	28	9.7	43	9.9	
LNR4 (≥0.40)	27	18.8	55	19.0	82	18.9	
Lymph Node Metastasis							0.610[a]
Yes	80	55.6	168	58.1	248	57.3	
No	64	44.4	121	41.9	185	42.7	
Distant Metastasis							0.110[a]
M0	138	95.8	265	91.7	403	93.1	
M1	6	4.2	24	8.3	30	6.9	
Staging							0.431[a]
I	19	13.2	41	14.2	60	13.9	
IIA	48	33.3	100	34.6	148	34.2	
IIB	12	8.3	19	6.6	31	7.2	
IIIA	6	4.2	10	3.5	16	3.7	
IIIB	39	27.1	83	28.7	122	28.2	
IIIC	15	10.4	16	5.5	31	7.2	
IV	5	3.5	20	6.9	25	5.8	
Degree of Staging							0.921[a]
Early stage (I-II)	79	54.9	160	55.4	239	55.2	
Advanced stage (III-IV)	65	45.1	129	44.6	194	44.8	
Lymphovascular invasion							0.314[a]

Negative	84	58.3	183	63.3	267	61.7	
Positive	60	41.7	106	36.7	166	38.3	
Perineural invasion							**<0.001[a]**
Negative	114	79.2	270	93.4	384	88.7	
Positive	30	20.8	19	6.6	49	11.3	

[a] Chi-Square; [a] Mann-Whitney; Percentage of the total column; NOS, nonspecific

We detected a significant difference in mean age (more than 23 years) between the young and old patient groups in **Table 3**. Additionally, the number of dissected LNs was substantially more remarkable in the young patient group than in their old patient counterparts.

Table 3. Comparison of the mean value of clinicopathological parameters of tumor between young and old patients

Parameters	Mean ± SD or Number			p-value
	Young patients (<50 y.o.)	Old patients (≥50 y.o.)	All patients	
CRC cases per year	54.91 ± 9.07	89.09 ± 10.94	144.00 ± 18.61	
Colon cancer cases per year	17.00 ± 6.93	34.45 ± 6.98	51.45 ± 13.05	
Rectal cancer cases per year	37.91 ± 5.20	54.64 ± 8.62	92.55 ± 12.40	
RSCRC cases per year	8.73 ± 4.10	16.82 ± 4.67	25.55 ± 7.15	
LSCRC cases per year	46.18 ± 7.04	72.27 ± 9.33	118.45 ± 14.69	
Age (years old)*	38.82 ± 7.46	62.01 ± 8.65	53.17 ± 13.94	**<0.001[a]**
Tumor size (cm)[#]	5.92 ± 3.12	5.99 ± 2.98	5.97 ± 3.02	0.818[a]
Smallest tumor size (cm)[#]	1.3	1.0	1.0	
Largest tumor size (cm)[#]	17.0	18.0	18	
Total count of positive LNs[#]	265	402	667	
Total count of dissected LNs[#]	1,587	2,726	4,313	
Positive LNs[#]	1.84 ± 3.37	1.39 ± 2.34	1.54 ± 2.73	0.107[a]
Dissected LNs[#]	11.02 ± 6.10	9.43 ± 5.04	9.96 ± 5.46	**0.004[a]**
LNR [#]	0.18 ± 0.29	0.18 ± 0.30	0.18 ± 0.29	0.964[a]

[a]Independent samples t-test for equality of means (2-tailed)

*Assessed among 1,584 patients

[#]Assessed among 433 patients

*Abbreviation: CRC, colorectal cancer; LNs, lymph nodes; LNR, lymph node ratio; RSCRC, right-sided colorectal cancer; LSCRC, left-sided colorectal cancer

Figure 5 describes the histopathological findings of our CRC cases, and the descriptive proportions are presented in **Tables 1, 2,** and **3.**

<**Figure 5.**>

Discussion

This observational study was conducted to assess clinical trends in CRC over 11 years, forecast the future burden of CRC over the next ten years, and analyze the pathology of 1,584 CRC cases recorded in a national referral hospital in Indonesia. The current investigation corroborated previous findings regarding men's predominance in CRC incidence. This could be because men are more likely to smoke and drink alcohol (both of which are risk factors for CRC), whereas women have higher levels of endogenous estrogens, which protect against CRC carcinogenesis.[36] Our study found that most CRC cases were identified in the middle-aged population, with the peak incidence occurring between 51–60 years old, consistent with previous findings.[37] Female patients had a mean age younger than male patients, consistent with findings from an investigation conducted in Brunei Darussalam.[38] The definition of "young patients"

in an epidemiological study of CRC is arbitrary; we used 50 years as the cutoff age since this is the recommended age for the first screening in most screening programs that have gradually gained global adoption.[15] Early-onset CRC is more likely to arise sporadically in third-world nations and hypothetically a biologically and clinically unique entity, accounting for its aggressive presentation and poorer prognosis.[39–41] We report that CRC incidence among young patients reached nearly 40%, significantly higher than the rate reported in a previous Indonesian study on CRC between 2014 and 2016 with 275 samples (31.3%),[42] Western countries (7%),[43] and other Asian studies (6.7–35.5%).[44,45] Other findings from South Asia were comparable to ours, with CRC incidence in young individuals ranging from 38% to 52%.[40,46] The increasing proportion of young patients in our population may well be influenced by the demographic profile of Indonesia, which had a high proportion of people aged 50 in 2019 (213,984,600 of 268,074,600; percentage: 79.82%).[47]

1. Trend Analysis of CRC

CRC incidence rates were modestly elevated in all patients and young patients with APC +2.23% and +1.98%, respectively, and the largest increase was statistically significant in subjects aged ≥50 years with APC +2.38% (p=0.041). Indonesia experienced a more significant increase in CRC incidence among old patients.[6] A similar conclusion was reached by Pham et al[48] in the Vietnamese (APC +5.3%; 95%CI 2.8–7.9%). We hypothesize that older patients are more likely to be included in incidentally and opportunistic screening programs than young patients. Since the population-based CRC screening program has not been implemented in routine clinical practice, the actual rate of early-onset CRC in Indonesia might have been undervalued. On the other hand, the estimated cost of treatment for CRC patients in Indonesia was up to $116,083.37,[49] representing 0.000011% of gross domestic product (GDP) in 2020.[50] The cost burden of treatment increases significantly as the disease progresses. In terms of screening costs, colonoscopy methods and fecal testing range from $207–765 and $2.75–11, respectively. Given the high cost of treatment and rising CRC incidence but the low cost of screening, our research suggests that Indonesia reconsider the benefits of a population-based CRC screening program for high-risk populations, particularly those born after 1980, to detect CRC earlier and reduce economic burden.

The WHO prediction for rising CRC incidence in Indonesia during 2020–2025 was higher than the APC of trend analyses in our results for CRC (+17.7% vs. +2.23%), colon cancer (+18.1% vs. +6.38%), and rectal cancer (+17.3% vs. –0.09%).[51] Also, our findings had a lower APC than a study conducted in Thailand among young patients between 1989 and 2012 (+5.7%)[52] and a study of all CRC patients in Tunisia from 1994 to 2009 (+3.9%).[53] Trend analysis in **Figure 2** reveals a sharp rise in colon cancer annually among young patients with a higher value of APC than old and all patients (+9.24% vs. +5.11% vs. +6.38%, respectively). In the last few decades, the incidence of CRC has been increasing in Asia and many Southeast Asia countries, including Indonesia and Malaysia.[54] If this trend continues, the number of CRC cases may suddenly overwhelm the healthcare system. Thus, better health policies should be constructed by the government.

The rise of CRC in young patients has not yet been fully elucidated. The early life of exposures to the deleterious effects of several risk factors has been thought increasing susceptibility to the CRC, such as frequent smoking, alcohol consumption, obesity, a Western lifestyle diet, a reduction in physical activity, and early-life antibiotic exposures. Smoking is associated with hypermethylation, microsatellite instability, and BRAF mutations in CRC carcinogenesis.[55] Smoking early in life plays a part in the high incidence observed in young Indonesian people due to frequent daily smoking in teenagers [13.4% (95%CI: 12.9–13.9%)] and youth [27.3% (95%CI: 26.8–27.8%).[56] The risk of CRC was also increased by alcohol

consumption, which had positive associations with the risk of distal colon cancer and rectum among the Asian population.[57,58] In Indonesia, alcohol consumption rose strikingly from 2000 to 2020, with the current proportion of alcohol consumption in teenagers [4.0% (95%CI: 3.8–4.3%)] and youth [6.4% (95%CI: 6.1–6.6%).[56] Obesity has been linked to a higher risk of colon cancer in Asians. This study reflected the conditions in Indonesia, where obesity also showed a high prevalence in the population aged 13–18 years (around 4–4.8%) and over 18 years [21.8% (95%CI: 21.7–22.0%)].[56,59] It is not surprising that the obesity epidemic and the rise in colon cancer happen simultaneously. Many behaviors that are thought to cause weight gain, like unhealthy eating habits and sedentary lifestyles, also raise the risk of CRC. Obesity can promote cancer formation through metabolic abnormalities, hyperinsulinemia, systemic inflammation, and alteration of the gut microbiota.[60] An upward trend in CRC in Indonesia is also probably due to the acquisition of the Western diet.[61] This lifestyle trend has been seen in Indonesian teenagers who consume inadequate amounts of protein, fruits, and vegetables, but excessive amounts of sodium and fast food.[62] A recent study found that the de novo introduction of a Western-style high-fat, low-fiber diet induces inflammation and proliferation in the colonic mucosa within two weeks.[63] Increasing obesity is approximately concurrent with reductions in physical activity levels.[64] A study in Japan found an inverse association between physical activity and CRC, and this association was stronger for colon cancer than rectal cancer.[65] This fact agrees with a survey in Indonesia that found 33.5% (95%CI: 33.3–33.8%) of the Indonesian population lacked physical activity according to time and frequency standards.[56] Another related risk factor among Indonesian is early-life and improper antibiotic use.[66] These early-life exposures and improper antibiotic use could change the gut microbiota and metabolic profile, and thus make people more likely to have obese later in life as one of risk factor for CRC.[67]

Almost two-thirds of the patients had rectal cancer, more common in the young (69%) than in old (61.3%) patients. The rectum becoming the most common site followed by the sigmoid colon is consistent with a previous study conducted in Saudi Arabia.[68] Instead of the proximal colon being a predominance site in young patients, the greater proportion of rectal cancer in our young patients implies additional factors behind these changes. Certain lifestyle factors relevant to young patients have contributed to colorectal carcinogeneses, such as processed meat consumption which is more linked to rectal than colon cancer.[69] We found that the rate of increase differed for colon and rectal cancer, ranging from 5.11% to 6.38% for colon cancer, compared with –0.97% to 0.58% for rectal cancer. In contrast to colon cancer, rectal cancer incidence has generally declined in overall patients and the young age group and remains stable in the old age group. These results may be because precancerous lesions or suspected tumors can be found and removed during a clinical examination of the rectum in screening.

This present study has not demonstrated the positive trend of rectal cancer as WHO predicted.[51] Although it will always be a predominant site for cancer, the incidence rate of rectal cancer appears to decline in young patients (–0.97%) and all patients (–0.09%) but is stable among old patients (0.58%). In Canada, after 1985, rectal cancer slightly declined, with an APC of –0.38% in the general population.[70] The trend of CRC subsite distribution progressively shifting to the proximal colon occurred in various countries, such as the US (1970–2000),[71] Japan (1974–1994)[72] and Norway (1962–2006).[73]

Our findings emphasize that the incidence of colon cancer rose faster than that of rectal cancer in young patients (APC +9.24% vs. –0.97%, respectively), similar to results among Canadian young patients from 1969 to 2010 (APC +6.2% vs. +1.5%, respectively).[74] The APC of colon cancer in our institution was higher than in Tunisia (+6.38% vs. +4.5%).[53] Some well-known risk factors do not exactly give a similar susceptibility between colon and rectal cancer. The carcinogenic process may be different depending on where it happens.[70] Diet patterns, physical inactivity, and high body mass index have been linked to a higher

risk of colon cancer, but not rectal cancer.[57,75] Meanwhile, smoking and alcohol consumption have been linked to a higher risk of rectal cancer than colon cancer.[76,77] Obesity, insulin resistance, and high blood glucose levels are connected to a higher risk of colon cancer because the colon is more insulin sensitive than the rectum.[78,79] It was also hypothetically that some participants benefited from a preventive effect against distal colon and rectal cancer, especially women. Endogenous hormones may have protected some women from developing colon cancer at the distal part and rectal sites, and increased use of exogenous hormones, such as hormone replacement therapy or oral contraceptives, may have resulted in further reductions in these cancers. Between 2005 and 2012, 61% of Indonesian women used contraceptive management.[80] This "preventative" effect has not been found in the proximal (right-side) colon tumors.[70]

In contrast to earlier findings and the widely held belief that RSCRC was always more common in young patients, our findings obtained more RSCRC frequent in old patients, supported by evidence from Germany.[81] Our results showed that most young patients had lesions in the left part of the bowel, higher than old patients, in agreement with a hospital-based study in the Memorial Sloan Kettering Cancer Center, in the US, where young patients were more likely to have LSCRC.[82] According to different cohort studies, RSCRC occurs predominantly in old patients, yet, worrisomely, LSCRC also occurs after 50 years of age, with a frequency more than that of RSCRC.[20]

Notable findings from the trend analysis in **Figure 2**. show that the APC of RSCRC rose statistically significant among all patients (+6.52%) and old patients (+6.57%) over the current eleven years period, and the largest APC was seen in young patients (+6.59%). The causes of these patterns are unknown; they might be due to, by nature, there was inconsistent plotting of several incidences each year to follow a particular joined line to figure out a trend. The rising trend of RSCRC from 2009 to 2019 could be influenced by a lack of genetic counseling addressing age, specific syndromes, and family history factors in Indonesia, as we know that RSCRC is more usually caused by genetic predisposition.[83] It is also challenging to detect nonpolypoid tumors (flat or depressed), more common in the right colon. These lesions are more likely to include carcinoma, are more difficult to detect, and occur more frequently in high-risk people.[84] Due to higher colonoscopy miss rates, these hazards may impede screening and identification of precancer and cancer lesions in the right-side colon, contributing to the rising trend of RSCRC.[85–87] RSCRC has a worse prognosis than LSCRC and rectal cancer.[88] A recent study found left-sided tumors to be increasingly observed in young patients, although not statistically significant among all (APC +1.41%), young (APC +1.37%), and old patients (APC +1.46%), similar to the report from Siegel et al.[89] The clinical implications of different proportion of side involvement between young and old patients was to the aggressiveness of the disease. RSCRCs are typically bulky, exophytic, polypoid lesions projecting into the lumen and causing significant anemia. LSCRCs are infiltrating, constricting lesions encircling the lumen, often leading to obstruction.[90] A study implied that LSCRCs are more genetically unstable and phenotypically more aggressive due to distinct molecular biology pattern between RSCRC and LSCRC in DNA-euploidy status, KRAS, and p-53 mutation rate.[81]

Observing more specifically the trend of colon cancer based on its subsites, what can be seen in **Figure 3** is the significant growth of 4 of 5 colon subsites during the study period. In our study, the APC of ascending colon rose more quickly than APC in China from 2000 to 2004 (+10.60% vs. +2.25%).[94] The transverse colon had the opposite results (+9.88% vs. –1.95%), the descending colon had different results (+10.04% vs. –1.02%), and the sigmoid had a more positive trend (+5.84% vs. +4.19%).[91] Surprisingly, no differences in APC were found in the caecum (–0.98%), which had a slow and steady decline in cases. These trends aligned with the right-sided dominance during the eleven years of study. Different parts of the colon may be more or less vulnerable to carcinogens because of biological differences in the intestine.[92] For

example, genetic factors may play a significant role in developing RSCRC, but factors like diet, exercise, and hormone use are more likely to be linked to a tumor on the left side.[92]

Trend analysis in this study enlightens us to identify patients in danger. Given the rapid economic transition and urbanization occurring in all areas of Indonesia, it is possible to generalize the upward CRC incidence trend in a single center in Jakarta to all of Indonesia,[93,94] similar to what a study suggested in Vietnam.[48] We need further research to see if the trend can be reversed, for example, by evaluating current CRC screening standards to lowering the age at which people begin screening. More studies are also required to investigate CRC risk factors in Indonesia to reduce the upward trend.

2. Forecasting the CRC Burden

In **Figure 3**, we forecasted the future burden of CRC by performing a fit-model regression analysis to predict colon and rectal cancer incidences along with RSCRC and LSCRC. The model with a significant slope was found in all patients in the colon, RSCRC, ascending colon, transverse colon, descending colon, and sigmoid colon. The model with a significant slope was found among young patients in only the colon. Meanwhile, the best-fitted model with a significant slope was found among old patients in CRC, colon, and RSCRC. The projection models of CRC, colon cancer, and rectum follow the exponential growth curve pattern in all and young patients, CRC and colon cancer follow the quadratic model in old patients, and rectal cancer follows the linear model. Compared to RSCRC, which follows the quadratic model, LSCRC was more varied, with all patients following the exponential growth curve, young patients following the quadratic model, and old patients following the S-shaped (sigmoid) curve.

Tailoring the best-fitted model for forecasting CRC cases in our institution had different clinical implications based on different curves. Addressing the interpretation of each curve was challenging since little robust research explains forecasting cancer incidence.[95] A linear trend is a forecasting model that develops a linear relationship between time and the response variable (incidence of disease). The linear model observed in rectal cancer among old patients means the cases gradually increase linearly at a constant rate over time. This model assumption was based on forecast accuracy metrics and supported by what has been pictured in trend analysis of rectal cancer with stable APC.[96] What should be highlighted in this paper is that although the rectum became the most prevalent site during eleven years, we identified negative trend or stable growth for this site in both Joinpoint analysis and fit-model regression analysis for forecasting, similar to what was reported in Japan (APC –1.9%; CI: –2.6% to –1.1%).[72]

Seven of fifteen scenarios were fitted into the quadratic curve model, a forecasting method that developed a non-linear relationship between time series and the response variable. The quadratic trend resembles a polynomial regression model that accurately captures the data trend.[96] All RSCRC follows a quadratic model, with a positive trend line of forecasting employed with all and old patients, meanwhile declining trend in the future for young patients. Forecasting of RSCRC remains upward for the trend until 2029 among all old patients. However, contrary to expectations, this study projected RSCRC to gradually decline in incidence for the next ten years (after 2019) in young patients following the quadratic model as a best-fitted model instead of continuously increasing over the previous eleven years. This assumption is similar to a study in the US, which found that RSCRC will increase, remain stable, and decrease by 2.3–2.6% annually.[83] The reasons for these conflicting findings remain unclear but might be explained by the complex attributions of risk factors on a different side of tumor involvement. It is possibly due to the increased use of colonoscopy and improved techniques and training for conducting colonoscopy in the right colon to screen, detect, diagnose, and these works will reduce RSCRC lesions among subclinical diseases in the future.[97] Another possible explanation for this result might be that in 2009–2019, a higher proportion

of patients having genetic factors resulted in a higher trend of RSCRC. Nevertheless, in the next ten years, we project that the trend will be shifting to increased distal cancer rates due to greater exposure to specific risk factors that cause cancers at these subsites, especially the increasing adoption of a Westernized lifestyle in Indonesia as in other Asian countries.[48,70,92,98,99] More interestingly, RSCRC among old patients is increasing significantly. This linear forecast is similar to the current literature, suggesting RSCRC is associated with several adverse prognostic factors: older age, advanced stage, and mucinous histological subtype.[20,100,101] We suggest that further studies are needed to find the associated factors for each CRC subsite in Indonesia to explain the subsite and side-involvement incidence trend.

Most cases followed the exponential growth curve as the best-fitted model. This curve has a J-shape, which refers to a growth whose rate is proportional to the size of the population over a specific period. Exponential growth curve modeling is a regression-based method for analyzing longitudinal data (i.e., tracking the same sample at different points in time), suited to the projection of trends in one disease entity like CRC into a different period. The advantage of growth curve modeling over other methods is that this technique permits the testing of several types of trajectories until the one with the best fit to the data is found, and an output is far more precise than other statistical means.[102,103] Exponential growth is distinguished by its slow start and, at some point, accelerating growth rate. The exponential growth curve has the fastest growth over the S-shaped, quadratic, and linear curves. This pattern causes an explosion of cases, relatively more than the S-shaped, which causes a relatively constant growth rate in the population.

One scenario of LSCRC among old patients following the sigmoid-shaped (S-shaped) curve trend model refers to a case whose growth rate decreases with the increasing number of individuals. It is a forecasting method that develops a sigmoid relationship between time and the response variable.[96] An S-shaped curve is symmetric around the inflection point, which means that the case increases initially rapidly, followed by a slower rate after the inflection point than the rate postulated by the curve. The cases following this pattern will have initial slow growth, then a growth explosion, and at their upper limit, they will be gradually steady. However, this can lead to under- and overestimating the actual disease risk at the lower and upper tails.[104] The S-curve trend model is best for time series that follow a logistic.[96]

Projected CRC cases in Indonesia for the next eleven years confirm the future global burden of CRC, which is expected to increase by 60%, to over 2.2 million new cases in 2030.[105] Looking specifically at **Supplementary Table 1** regarding the cases predicted for 2020–2029, it implied to us that the burden of CRC remained high in our institution and that this trend might apply to all of Indonesia.

3. Distinct Clinical and Pathological Features in Young Patients

Genetic mutations and lifestyle changes may be to blame for the spread of CRC in young patients. Molecular profiles of Indonesian CRC cases are found to progress in distinct pathways.[8] Our young cases, mainly found in distal locations for CRC, are not in line with the characteristics of hereditary CRC, primarily found in proximal sites. They also did not follow the conventional pathways of sporadic CRC (the CIN pathway). Instead, it is mixed with MSI and inflammatory pathways, including cyclooxygenase-2 (COX-2) and nucleus factor κB (NF-κB). Also, lower mutation rates of the pro-oncogene KRAS are found among young Indonesian patients.[8] Sudoyo et al[106] obtained 56.5% of CRC cases positively stained for MSH2 and 16.5% stained for MLH1. Moreover, signet-ring cell carcinoma—an aggressive subtype of CRC that spreads rapidly and is characterized by late symptom manifestations—disproportionately affects young individuals.[107] It is also possible that the differences in the immune systems of young patients could play a role in age-related immunosenescence, T-cell dysfunction, and systemic inflammation.[108]

The impact of age is crucial due to their prognosis. Although the results were still inconsistent, some suggest worse outcomes,[109,110] whereas others imply equal prognosis between the two groups[111] depending on staging reported.[37,110] Contradictive to other studies,[40,112,113] where stage III-IV predominate in the young age group, we showed more than half of our young patients are found in stage I-II. However, our study reported no statistically significant difference in advanced disease between young and old patients, similar to a prior investigation.[114] This might reflect increased awareness of the disease among both patients and primary care physicians, better access to colonoscopy, and more widespread use of CT with improved quality. Also, the introduction of national health insurance in the middle of the study period (2014) made access to healthcare more accessible, increasing people's concern for their health. Providing better facilities for cancer diagnosis may result in an inflation of the prevalence number of CRC and earlier detection of CRC with a screening program.[115] Cancer patients found through screening show up at a much earlier stage of the disease than those not found through screening. Our study found no distinct clinical characteristics between young and old patients in sex, side involvement, proximalization, or specimen type. There is no tendency for proximalization of colon cancer in young patients compared to old patients in our study. Overall, the proximal and distal colon had an equal proportion. However if we included rectal cancer in the calculation of distal CRC, the proportion was aligned with an extensive colonoscopy survey in Asia, which found that more patients had distal than proximal CRC.[116]

Single-institution and population-based studies have found that young patients with CRC have unique tumor locations, stages at presentation, and histologic features. Our findings are similar to those of these studies.[117–120] The proportion of rectal cancer among young patients was significantly higher than in old counterparts, as previously mentioned in Americans, where 32% of CRC tumors occurred in the rectum.[120] Looking more specifically at colon subsites, young patients with CRC mainly originate from the ascending and descending colon. Meanwhile, the caecum, transverse colon, and sigmoid were the most affected sites among old populations. People who have poor-defined histologic features, such as mucinous and signet ring features, are usually more likely to have poor outcomes in CRC.[109] They are also more resistant to chemotherapy.[114] Our results showed that the proportion of adenocarcinoma NOS in young patients is less than in old ones, agreeing with a study by Chan et al[43] (84% vs. 92%, respectively) and Gheju et al[121] (86.7% vs. 84.7%, respectively). The mucinous histological variant was significantly higher in the young than in the old patients. Signet-ring cell cancer was only observed in young patients, accounting for only 0.6–1.0% of all CRC cases globally.[121] Our patient who has signet-ring cell has the following characteristics: the average age of 48 years old, female sex, location in the caecum, right-sided, size 5.5 cm, brown color surface, exophytic, LNR 5/13 (adequate), pT3N2aM0 (IIIB), negative LVI, negative PNI, and having poor differentiation of the tumor. However, instead of being among young patients, only one patient with signet-ring cell carcinoma was found in the Romanian study, and that patient was >50 years.[121] Signet-ring cancers have intracellular mucin pushing the nucleus to one side and are associated with a more advanced stage at diagnosis, a higher incidence of LVI, LNM, and liver metastases, a higher rate of recurrence, and more aggressive.[122,123] The literature stated that mucinous histopathology was a significant predictor of poor outcomes and more advanced node stage.[124]

The average number of dissected LNs in our study was lower than in a recent Romanian study (9.96 ± 5.46 vs. 35.7 LNs removed), indicating that optimal LNs sampling was challenging to yield in our institution.[121] Meanwhile, the average number of positive LNs per patient was lower than positive cases in Romania (1.54 ± 2.73 vs. 3.7 (1–62)).[121] The interpretation of LNM is thus more complicated because the number of dissected LNs was not ideal, but the positive number was satisfactory. More insufficiently removed LNs resulted in a higher probability of positive LNs in actual condition due to unsuccessful LNs

taking, which could be harmful to cancer spread. This issue will have a significant impact on patient staging. In contrast, increasing the number of dissected LNs leads to more accurate information about node status and the best treatment for patients. In a recent Dutch nationwide study,[125] the authors found that with an increasing number of evaluated nodes, the risk of death is decreased, related to a better quality of surgical resection (yielding more LN for the pathologist to assess).

A closer inspection of the dissected LNs in **Table 3** shows significant differences between the two age groups. The number of adequate LNs dissection in the young patients was higher than in old patients showing a favorable finding in young patients. Old patients are more likely to receive inadequate LNs dissection during operative therapy. Old patients are at a higher surgical risk for various postoperative complications and their comorbid diseases, possibly making surgeons consider the risks and benefits of a more thorough LNs dissection.[126] The number of LNs dissected from resection specimens depends on several factors, including the surgeon's technique, bowel resection length, and tumor location.[127] The data supporting a minimal LN count of 12 is problematic, and a more realistic and practical LNs count should be measured using LNR, a positive LNs ratio to dissected LNs. Our average LNR was 0.18 ± 0.29, which was lower than a prior study in Romania (0.221 (0.139–1)),[121] which were more insufficient but had fewer positive LNs, presumably resulting in a lower class for LNR. LNR provides a superior prognostic power than the number of positive nodes alone and is significantly associated with poor survival of CRC.[128] However, given the absence of difference between the two age groups, it is advised that LNR be included as a predictive indicator in future CRC staging systems for all patients.

We found a tiny proportion of PNI in all patients than in the Elsamany et al[129] (11.3% vs. 24.4%) study. However, we found a higher proportion of PNI in the young patients than in the old patients, similar to a study by Zahir et al[39], showing that 22% of young patients with CRC had positive PNI. The presence of PNI is associated with a higher rate of metastatic disease, recurrence, and reduced survival. Several studies have recognized it as a notable independent prognostic factor in CRC multivariate analysis.[130]

Although some pathological features had significant differences between the two age groups, no evidence was found for significant differences in tumor size, growth pattern, tumor grade, pT, pN, LNR, LNM, distant metastasis, and LVI. Two-thirds of patients are found with tumor size ≥5 cm, even with the largest size of 18 cm. Although some authors believe that tumor size does not affect prognosis, others believe that tumor size partially influences prognosis.[131,132] Increasing tumor size is associated with decreased loco-regional control, resulting in the increased risk of its malignant potential.[133] Bigger tumors are more likely to be more profoundly invasive and invade neighboring organs.[134] Local recurrence was significantly higher in patients with tumors measuring ≥5 cm in size, poorly differentiated adenocarcinoma, pT4 stage, and having adjuvant radiotherapy. Moreover, the 5-year overall survival rates in the patients having tumors with size ≥5 cm were lower than those in sizes <5 cm, respectively (log-rank, p=0.001).[135]

According to our findings, the proportion of growth patterns was (from highest to lowest) exophytic in both age groups, followed by endophytic, linitis plastica, and ulcerative. These findings agree with a previous study in Thailand, which found fungating and polyp mass (exophytic) were higher than ulcerative mass.[135] Our study demonstrated that a more common growth pattern is exophytic or polypoid growth (85.2%), which tends to be higher in old patients than in young patients (87.9% vs. 79.9%). Ulcerative and linitis plastica were scarce in number, which is favorable since both growth modes entail a worse prognosis. A linitis plastica suggests de novo origin, associated with a reduced proportion of KRAS mutations. Clinically, de novo tumors may represent a more aggressive subtype of CRC with poorer prognosis disease progression and higher aggressiveness.[90] These results call for more awareness and persistence in detecting

non-polypoid lesions, more intensive monitoring of colonoscopically treated cases, and surgery for selected patients.

Related to tumor grading, in both age groups, most tumors were well-differentiated, similar to a study in India.[124] These findings differed from those of a study by Chan et al[46], who discovered that both age groups were primarily affected by cases of moderately differentiated tumors. We found that young patients were more likely to have poorly differentiated CRC than older patients. This finding shows how aggressive tumor biology is in young patients and implies a poorer prognosis regarding distinct differentiation and histological subtypes distribution.[110,136] However, despite significant results in histological subtypes, we found no significant difference in tumor grade in our patients.

Another adversely impacting prognostic feature, LVI, was detected less frequently in our study (38.3%) compared to a previous report.[129] However, the proportion of positive LVI was higher in young patients than in old ones (41.7% vs. 36.7%). These results show that LVI is an important histopathological feature in young patients to assess in every young patient with CRC.

In short, all the empirical findings relating to clinicopathological characteristics of CRC in this study have provided a new understanding of this disease entity in Indonesia. Our study collected CRC archives from one of the national referral hospitals for cancer with the most extended span period. Its coverage could represent CRC epidemiology on a regional scale since primary data for the whole country is not readily available. However, we face several constraints during this study—for example, the retrospective design in which the quality of the database depends on the patient records. We may also have missed some old, frail patients with symptoms of CRC who were treated at home or in nursing homes without further investigation. Furthermore the projections of future CRC incidence discussed in this study should be carefully interpreted.[95] Predictions of future cancer incidence inherently depend upon several uncertain factors, could be part of a larger cycle, and may not persist into the future. Our projection of CRC in 2020–2029 was assumed to have similar clinicopathological characteristics as the circumstances observed from 2009 to 2019. Change of certain factors in the population or the presence of new emerging public health threats (i.e., pandemic) may influence the record of a predictive number of cases. Trends and projections can be volatile, and thus we can only forecast cases over a short span of period. Furthermore, this work does not include population-level data, and the mathematical prediction of cases in this study should be further validated using multicenter data. Despite these constraints, our data showed a similar trend to other countries worldwide, particularly Asian countries, and the incidence rates fit well into forecasting models, allowing clinicians and policymakers to predict and anticipate future disease burdens.

Conclusion

This study set out to assess clinical trends in CRC over 11 years based on tumor locations and side involvement, forecast the future incidence of CRC for ten years, and analyze the clinicopathological profile of CRC among the Indonesian patients in a single center. Epidemiological trends and forecasting of CRC cases in Indonesian patients showed an enormous increase, notably for colon cancer, with a particularly concerning trend in young patients. Forecasts for the next ten years using fit-model regression analysis found a significantly high number of CRC burdens in the future, particularly in the colon, compared to rectal cancer cases, which are stable and declining. Additionally, young patients exhibited particular clinicopathological characteristics regarding tumor location, tumor subsites, histological subtypes, adequacy of dissected LNs, and PNI contributed to the disease's severity, aggressiveness, and prognosis. Multidisciplinary policies encompassing specialized screening protocols, extensive educational efforts, and lifestyle adjustments are required immediately to address this perplexing problem.

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Contributors

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Competing interests
None declared.

Patient consent for publication
General consent was obtained from the patient for the use of medical record data and residual specimens on admission, as conforming with the ethics approval (details below)

Ethics approval
This study has been approved by the Institutional Ethical Review Board (ERB) of the Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangkunkusumo Hospital, Jakarta, with the ethical approval number: KET-139/UN2.F1/ETIK/PPM.00.02/2020 and protocol number: 10-11-1416. The chart of cancer registry data was anonymized before the authors gained access to it for this study.

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Data availability statement
All data relevant to the study are included in the article.

Supplementary Information

- **Supplementary File 1. Trend Analysis of All Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement
- **Supplementary File 2. Trend Analysis of Young Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement
- **Supplementary File 3. Trend Analysis of Old Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among old patients based on tumor location and tumor side involvement
- **Supplementary File 4. Forecasting Analysis of All Patients**
  Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among all patients based on tumor location and tumor side involvement
- **Supplementary File 5. Forecasting Analysis of Young Patients**
  Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among young patients based on tumor location and tumor side involvement
- **Supplementary File 6. Forecasting Analysis of Old Patients**
  Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among old patients based on tumor location and tumor side involvement
- **Supplementary Table 1. Summary of Forecasted Cases 2020-2029**
  Description: Summary of a best-fitted model, predicted case equation, and number of forecasting cases during the period between 2020 and 2029

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Figure Legends

Figure 1. Study flow diagram for retrospective data collection, selection process, analysis of the overall included sample, and subanalysis of complete data in the final report

Figure 2. Trend analysis using Joinpoint regression expressed by annual percentage changes (APC) of colorectal cancer incidence among 1,584 patients during eleven years period of study counted by tumor locations (colorectal, colon, and rectum), and side involvement (right-sided and left-sided colorectal cancer) grouping by all, young, and old patients. Colon plus rectum indicated a total incidence of both locations. A positive trend for 2009-2019 was observed among colorectal, colon, right-sided, and left-sided cancer, while rectal cancer tended to be stable and more decreasing in all young and old patients. Plotted lines indicate APCs. *Indicates that the APC is significantly different from zero at the alpha = 0.05 level using the logarithmically transformed data permutation model in Joinpoint regression analysis.

Figure 3. Tumor subsites specific incidence rate using Joinpoint regression expressed by annual percentage changes (APC) of colorectal cancer incidence among 1,584 patients during 2009-2019 based on anatomical subsites of tumor in the colon in all patients. A sharp increment of cases by order in value was found in ascending, descending, transverse, and sigmoid colon, while a gradual decline was observed in the caecum.

*Significant change in APC versus 0 (P <0·050) using the logarithmically transformed data permutation model in Joinpoint regression analysis.

Figure 4. Annual incidence trends, the equation for predicting cases, and the forecast number of cases in the next-ten year using the best fitted-model regression analysis (linear, quadratic, exponential growth, or S-shaped curve model) for colorectal cancer counted by tumor locations (colorectal, colon, and rectum), and side involvement (right-sided and left-sided colorectal cancer) grouping by in all, young, and old patients. Projection of positive trend for period 2020-2029 observed among colorectal, colon, and left-sided cancer while rectal cancer tended to be stable and more decreasing in all, young, and old patients. Right-sided colorectal cancer was forecasted increased burden in all and old patients but tended to decrease in young patients. *Indicates significantly progression slope ($p<0.05$; ANOVA statistical test); Blue straight connected points show actual rates, red loosely dotted connected line indicate a best-fitted trend, and green densely connected dotted line point the forecasting trend. Y_t is the variable (equation for predicted cases), and t is the value of the time unit (year). **Abbreviation**: CRC, colorectal cancer; MAPE, mean absolute percent error; MAD, mean absolute deviation; MSD, mean square deviation.

Figure 5. Histopathological features of colorectal cancer resection specimen (all in HE staining). (a) well-differentiated adenocarcinoma NOS (M40x); (b) poorly differentiated adenocarcinoma NOS (M40x); (c) mucinous adenocarcinoma (M40x, inlet 100x); (d) signet-ring cell carcinoma (M40x, inlet 400x); (e) pT2 stage tumor infiltrating muscular layer (M40x); (f) pT3 stage tumor infiltrating adipose tissue in sub-serousal layer (M40x); (g) lymphovascular invasion (pointed by red arrow, M40x); (h) perineural invasion (highlighted by yellow arrow, M40x); (i) lymph node metastasis (M100x)

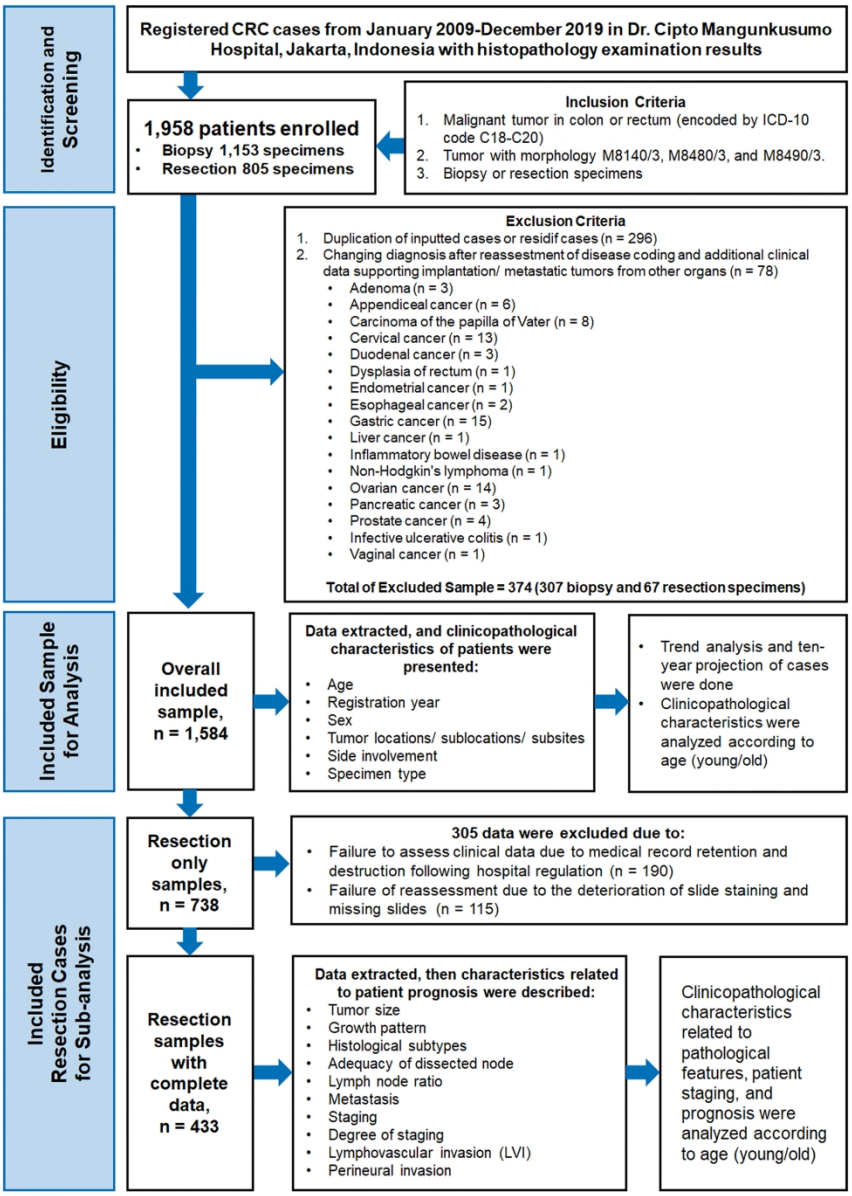

Figure 1. Study flow diagram for retrospective data collection, selection process, analysis of the overall included sample, and subanalysis of complete data in the final report

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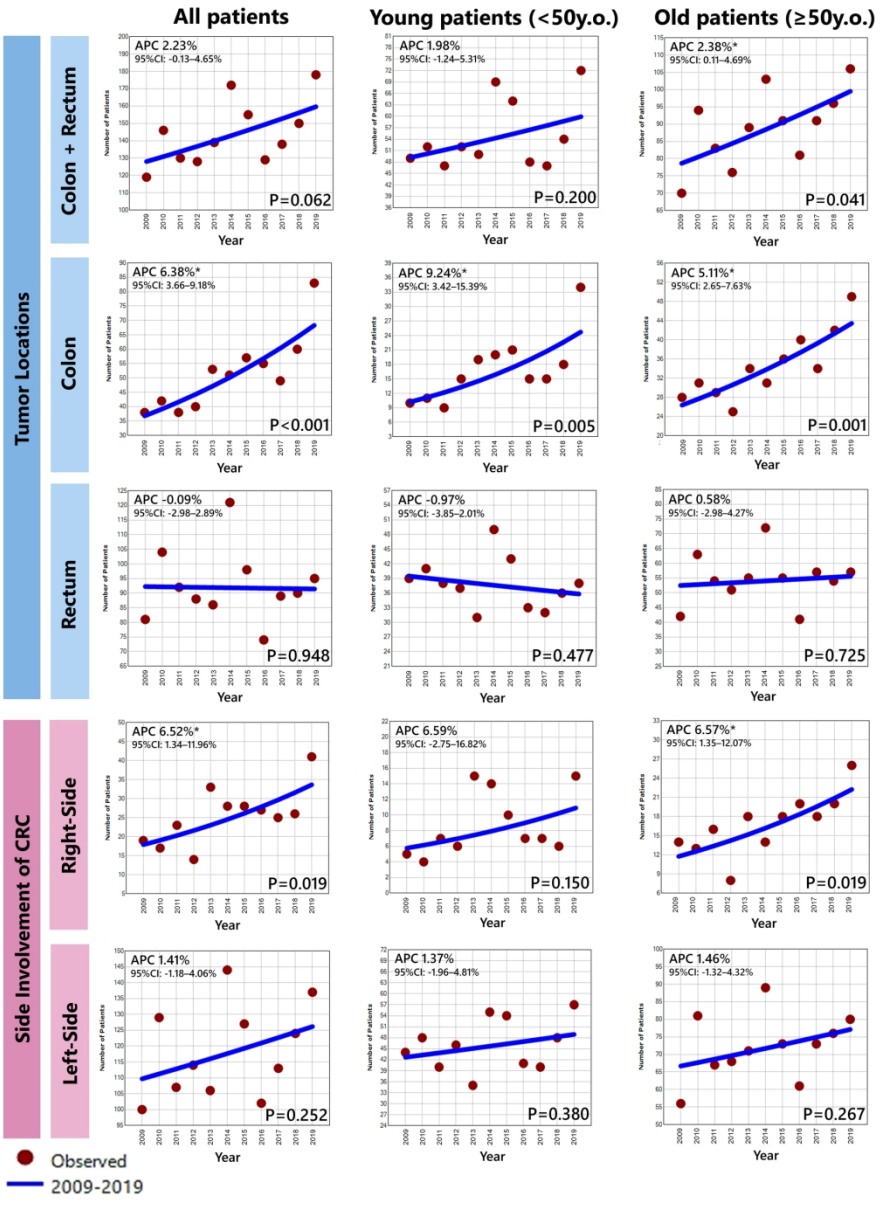

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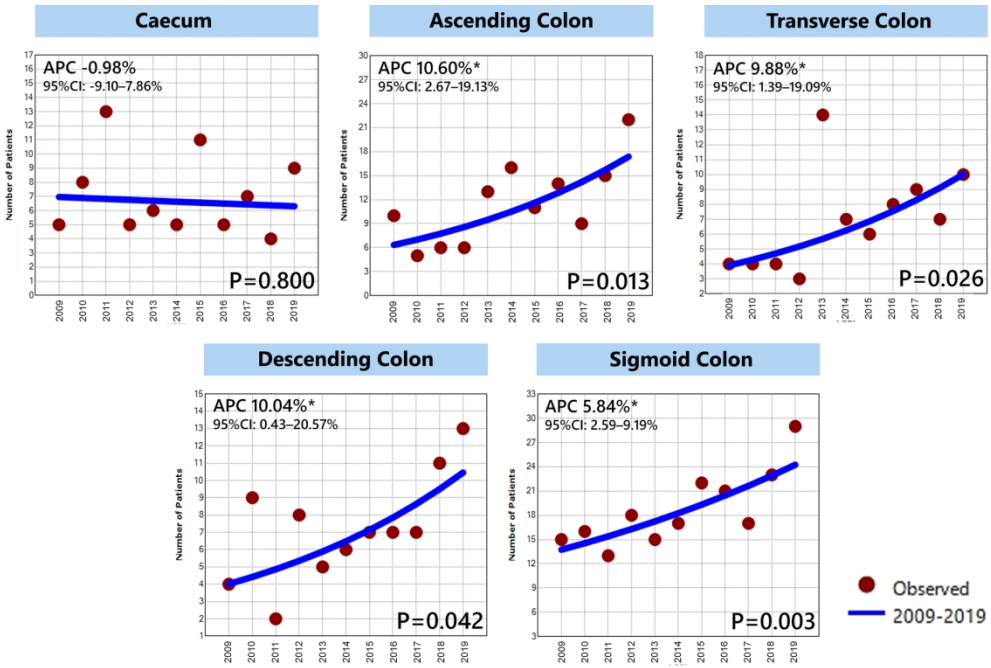

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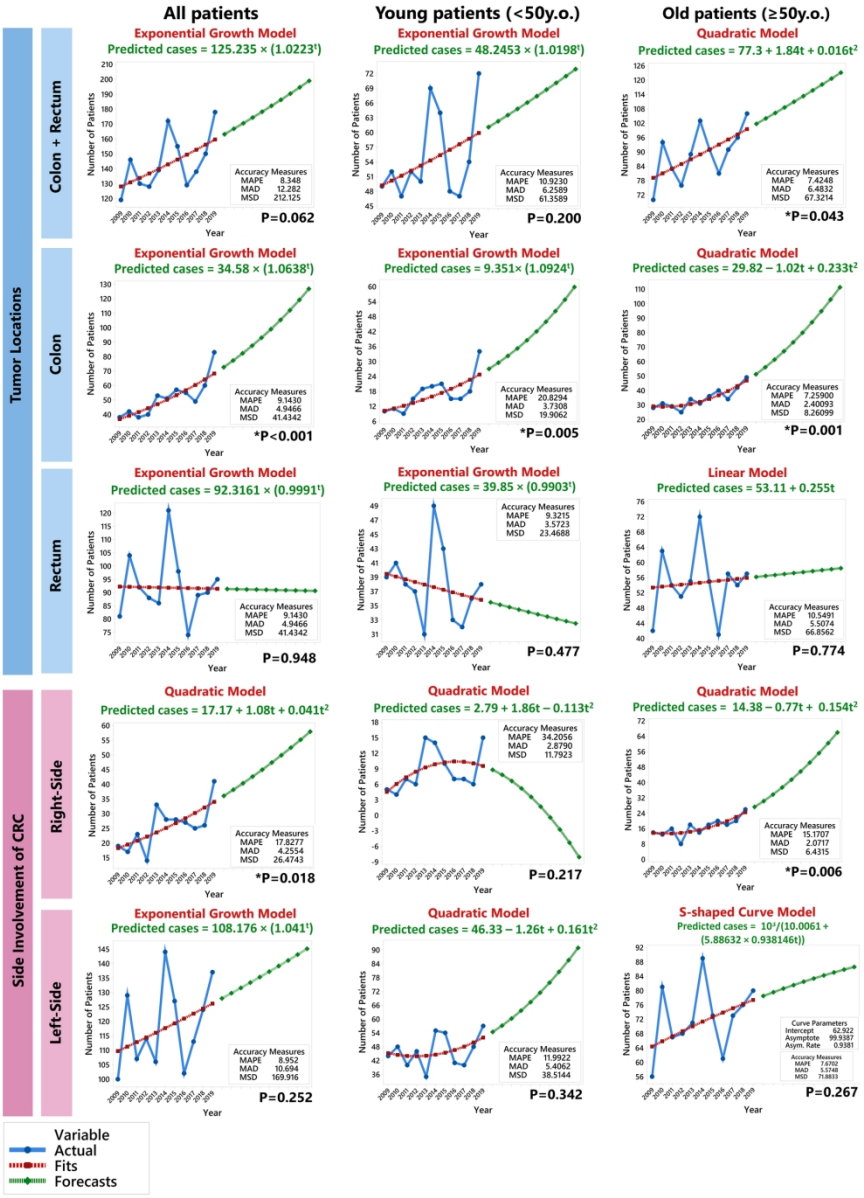

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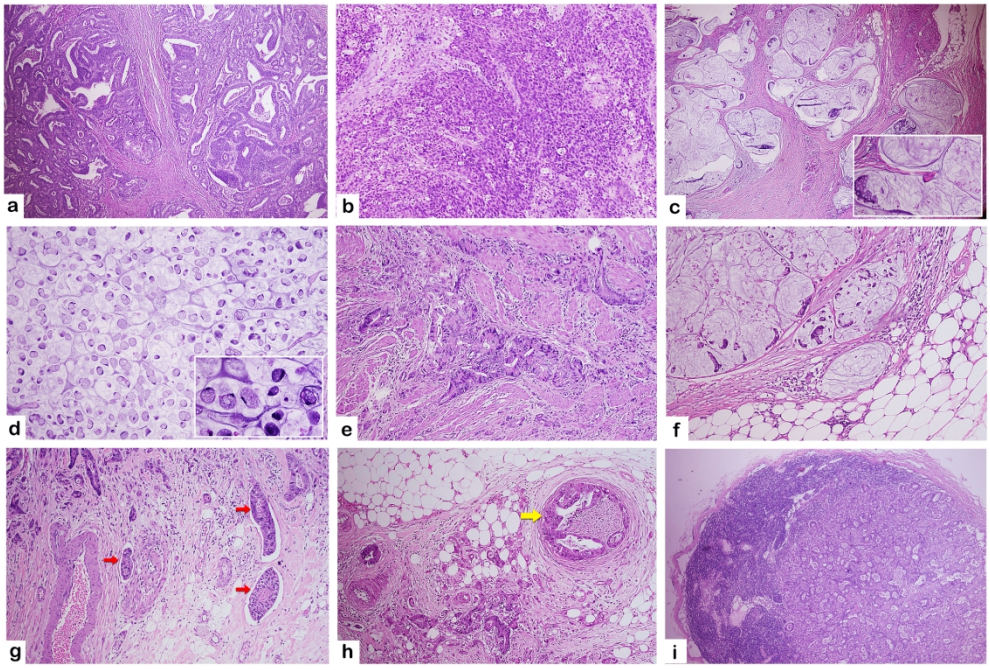

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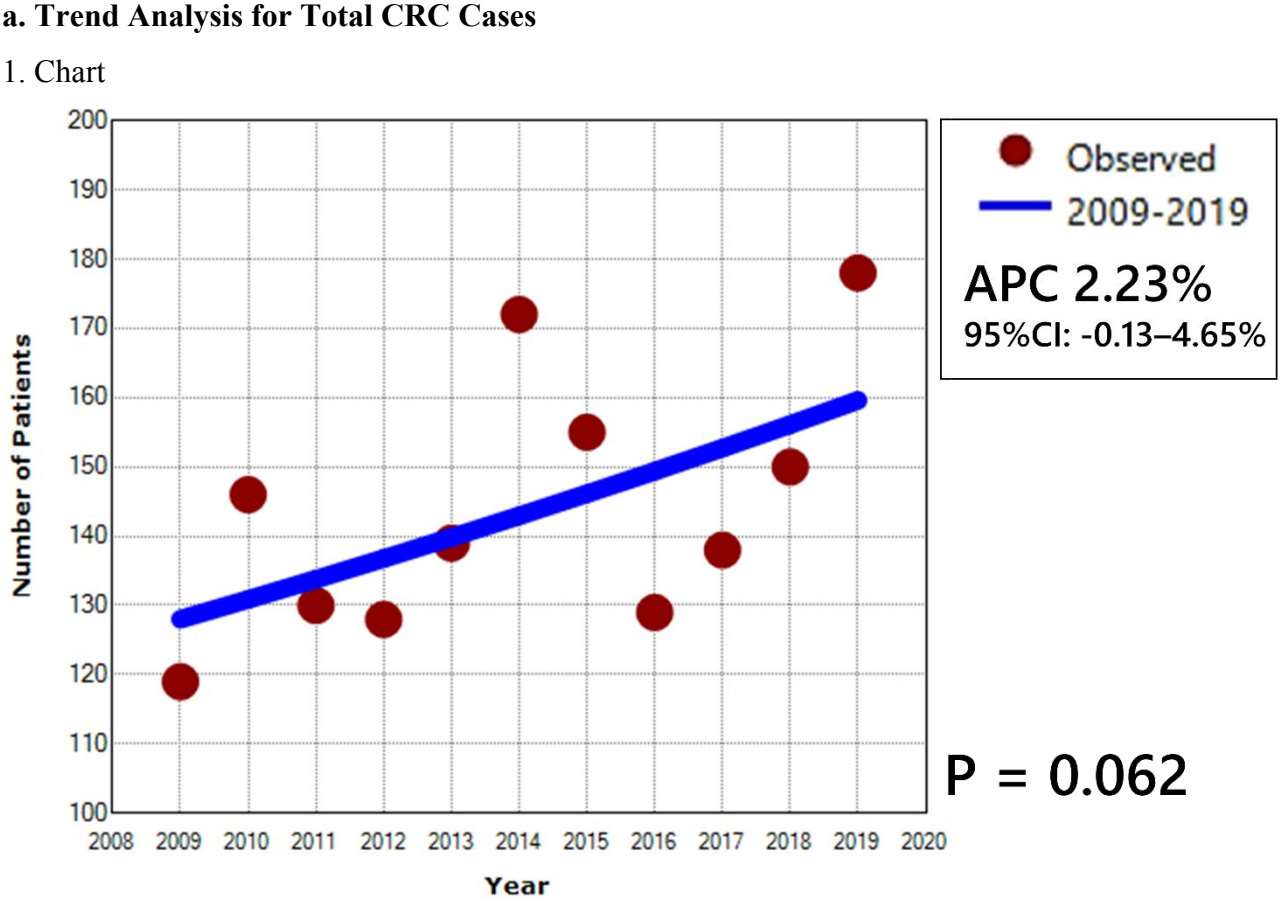
Supplementary File 1.

Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement

a. Trend Analysis for Total CRC Cases

1. Chart

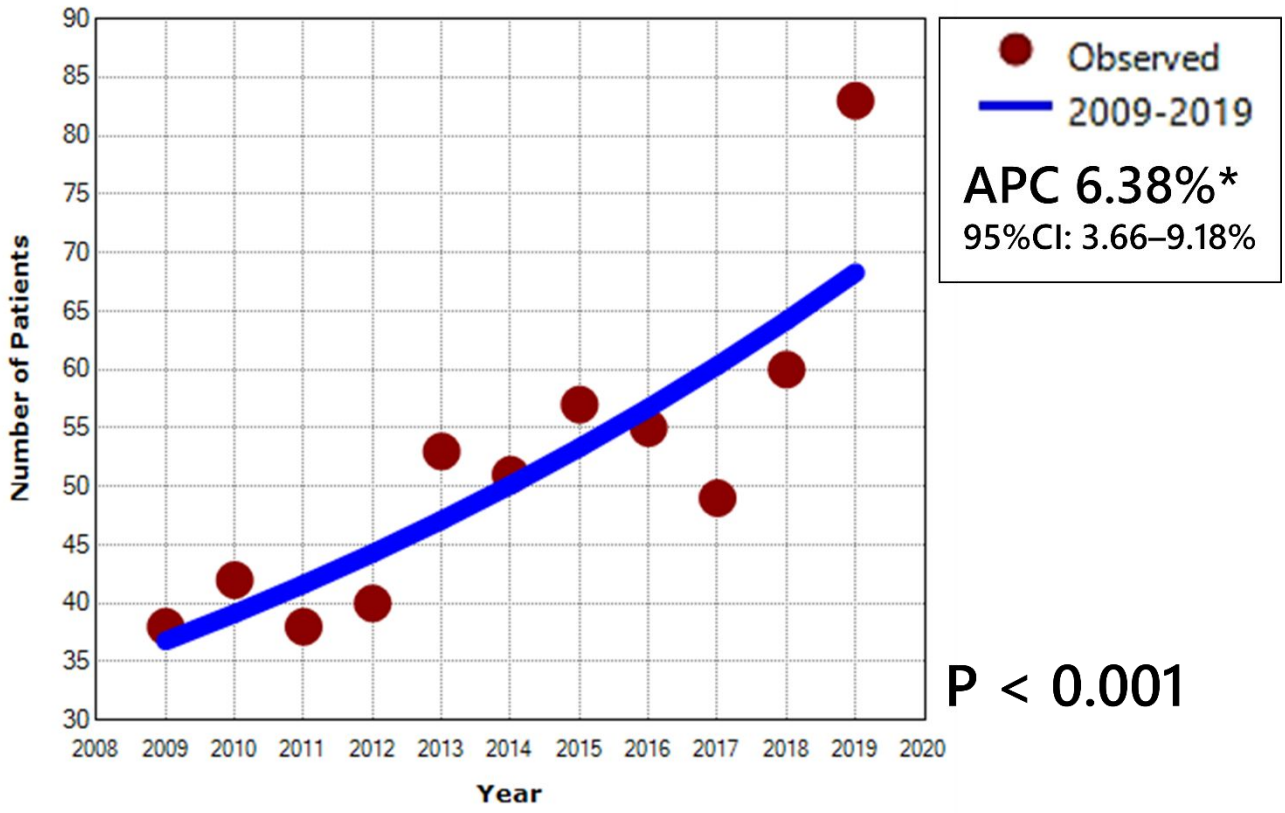


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	2.23	-0.13	4.65	2.13	0.062
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	2.23	-0.13	4.65	2.13	0.062
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Total Colon Cancer Cases

1. Chart

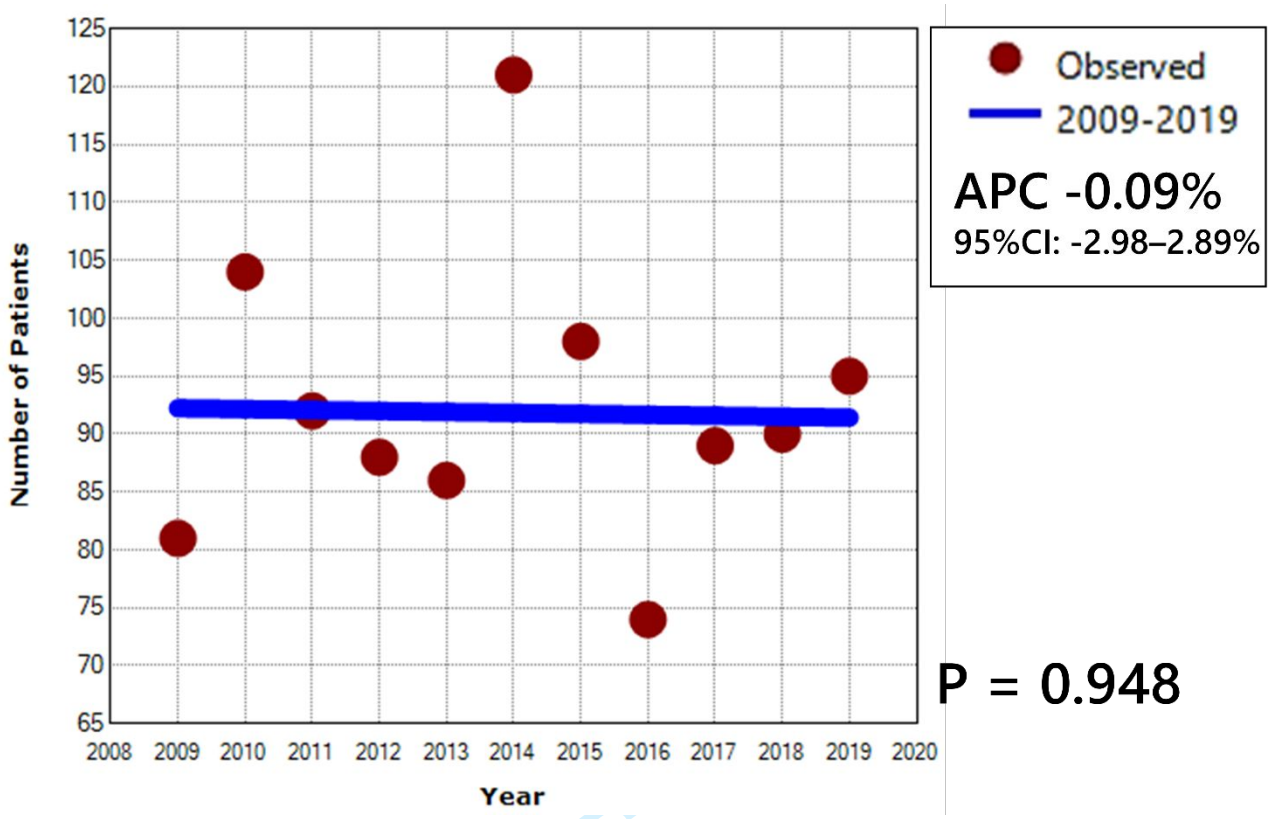


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.38*	3.66	9.18	5.39	< 0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.38*	3.66	9.18	5.39	< 0.001
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Total Rectal Cancer Cases

1. Chart

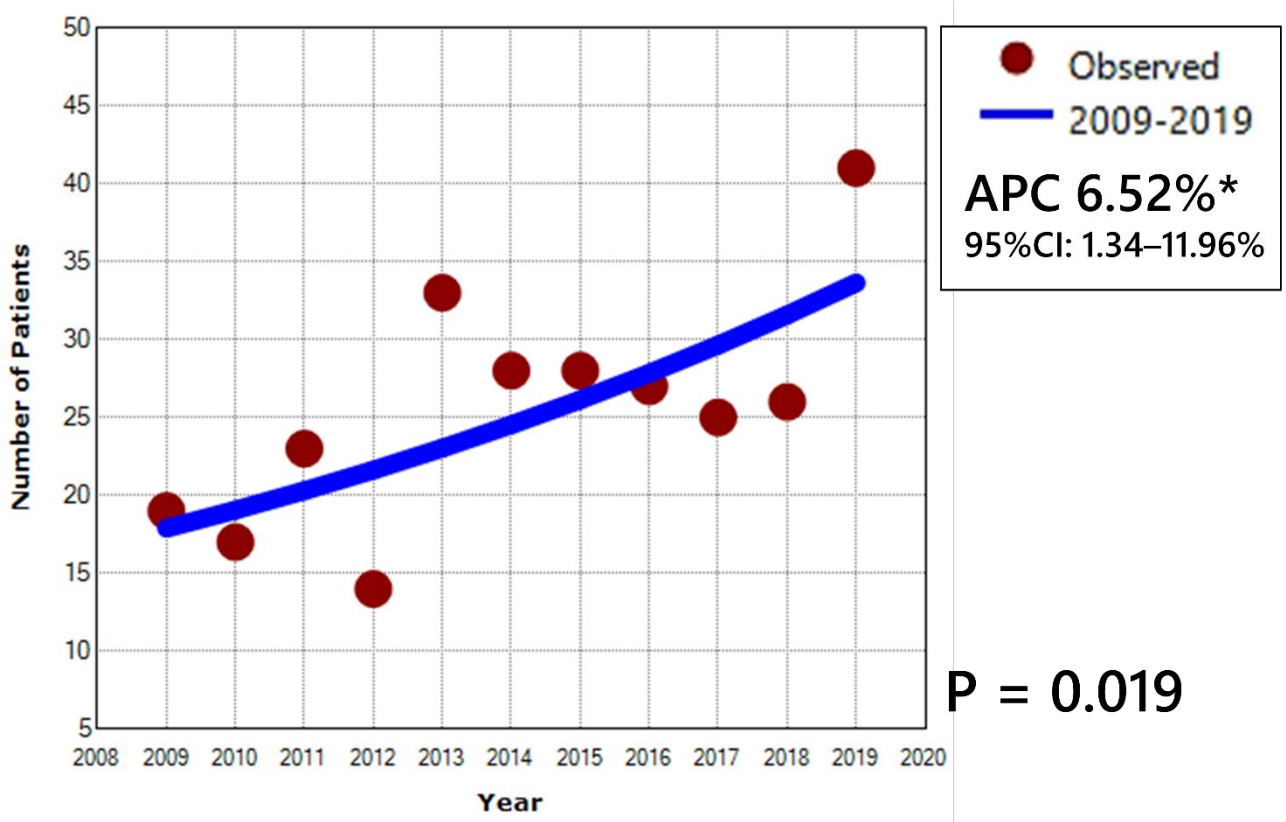


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.09	-2.98	2.89	-0.07	0.948
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.09	-2.98	2.89	-0.07	0.948
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Total Right-Sided CRC Cases

1. Chart

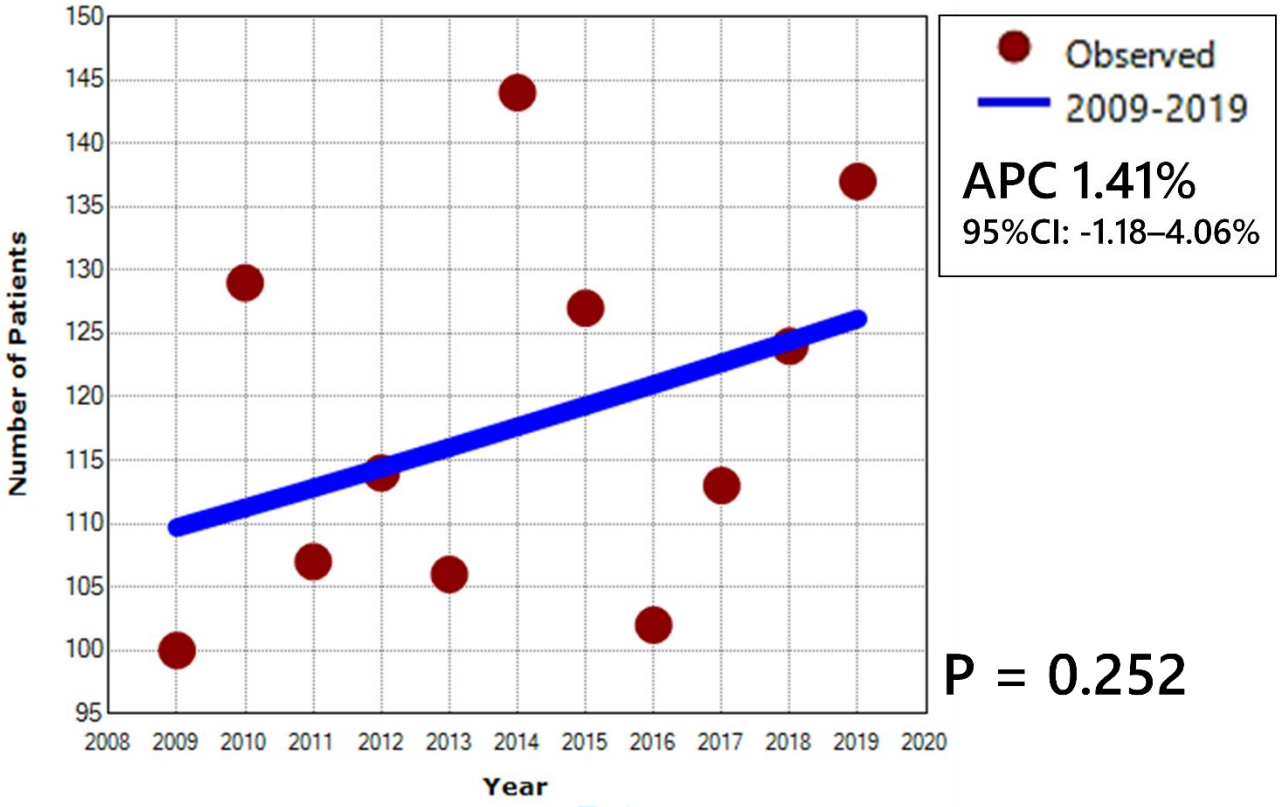


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.52*	1.34	11.96	2.87	0.019
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.52*	1.34	11.96	2.87	0.019
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Total Left-Sided CRC Cases

1. Chart

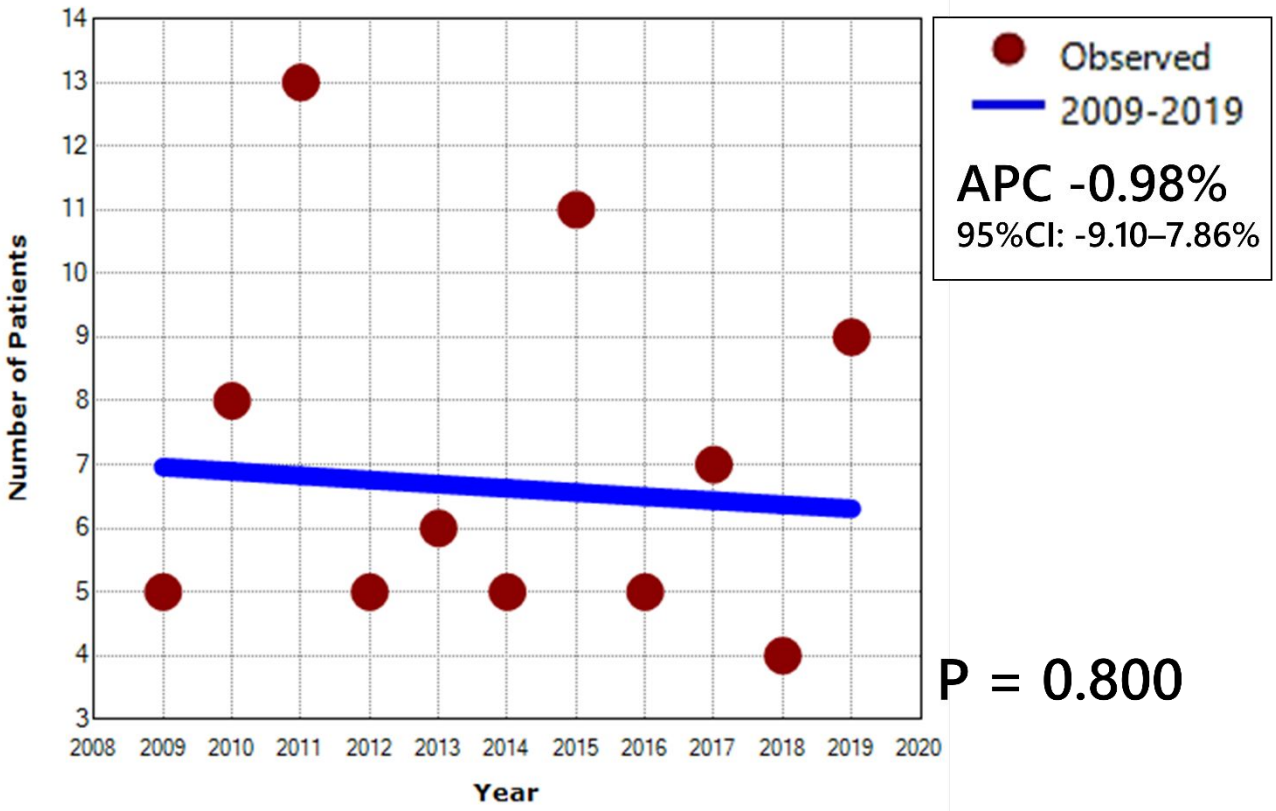


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.41	-1.18	4.06	1.23	0.252
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.41	-1.18	4.06	1.23	0.252
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

f. Trend Analysis for Total CRC Cases Originated from Caecum

1. Chart

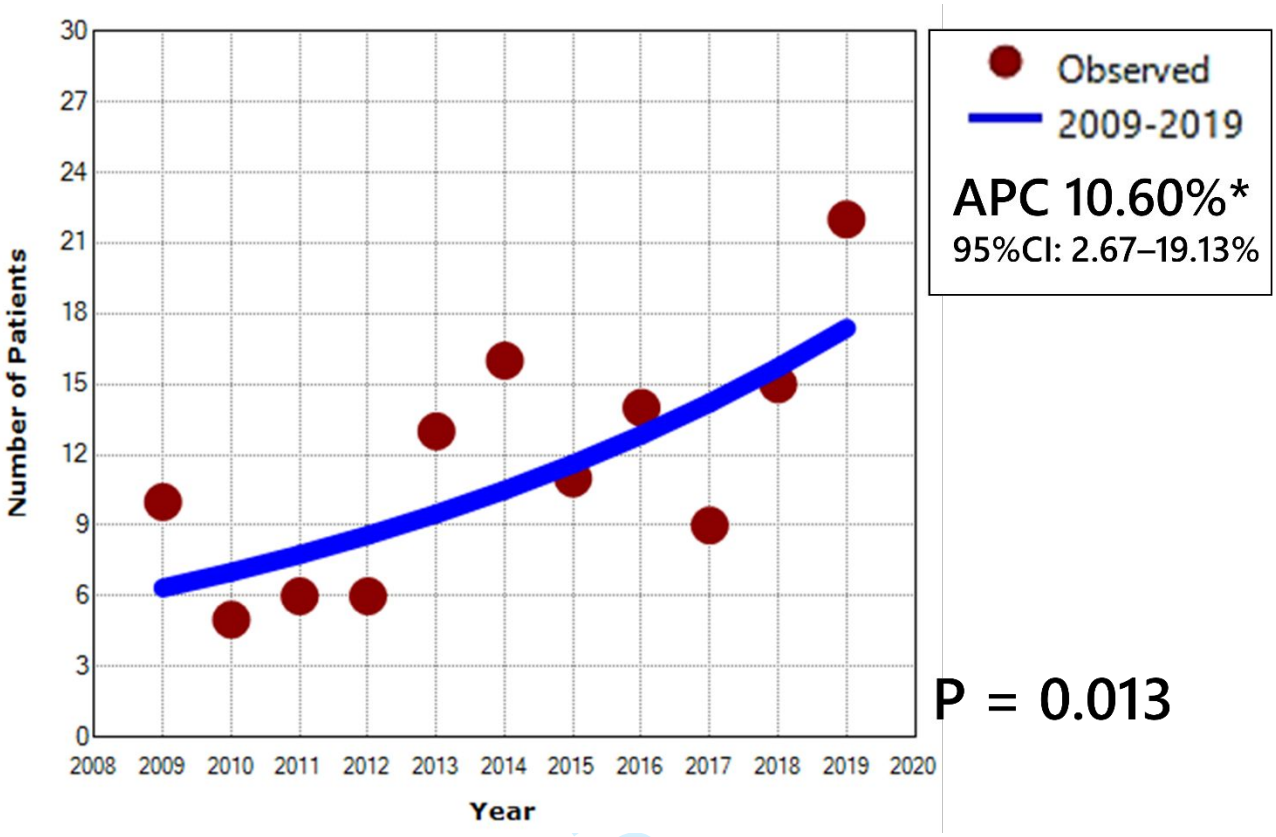


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.98	-9.10	7.86	-0.26	0.800
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.98	-9.10	7.86	-0.26	0.800
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

g. Trend Analysis for Total CRC Cases Originated from Ascending Colon

1. Chart

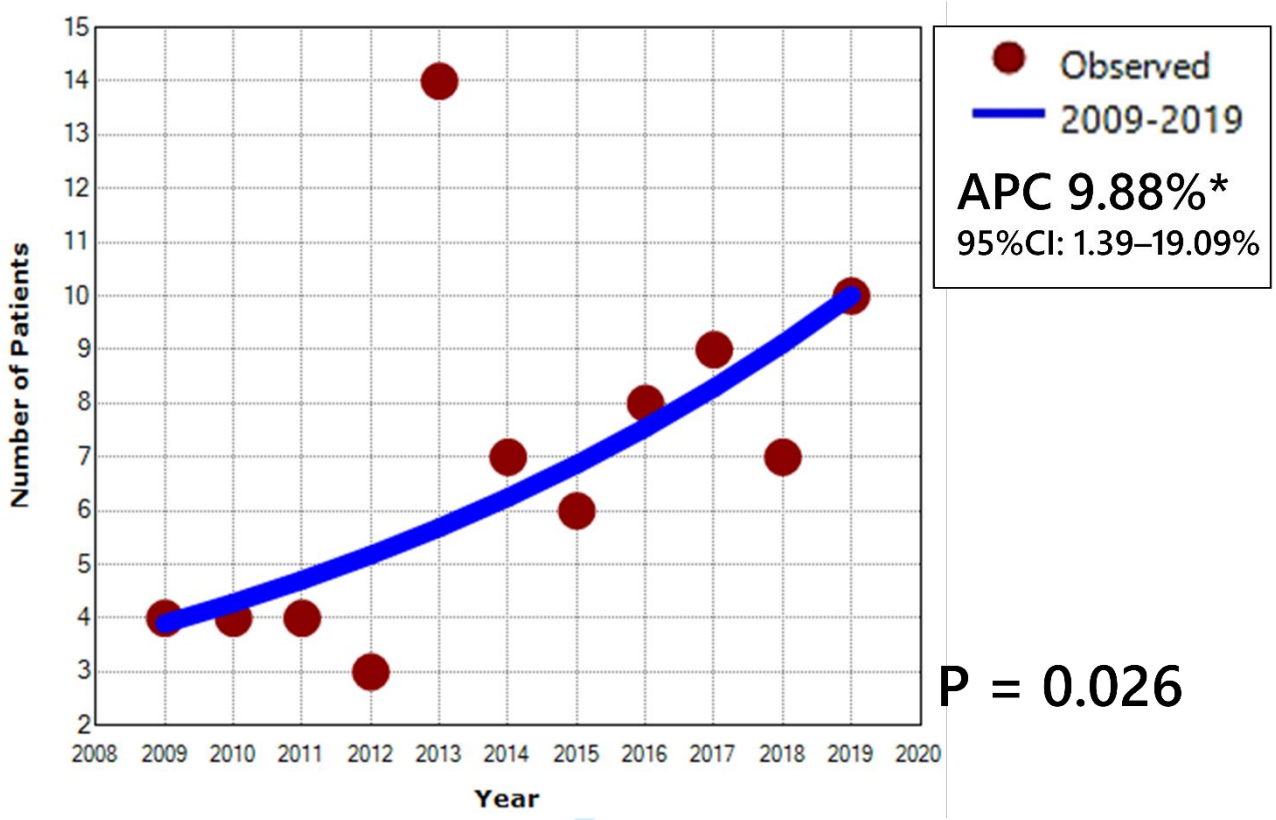


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	10.60*	2.67	19.13	3.07	0.013
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	10.60*	2.67	19.13	3.07	0.013
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

h. Trend Analysis for Total CRC Cases Originated from Transverse Colon

1. Chart

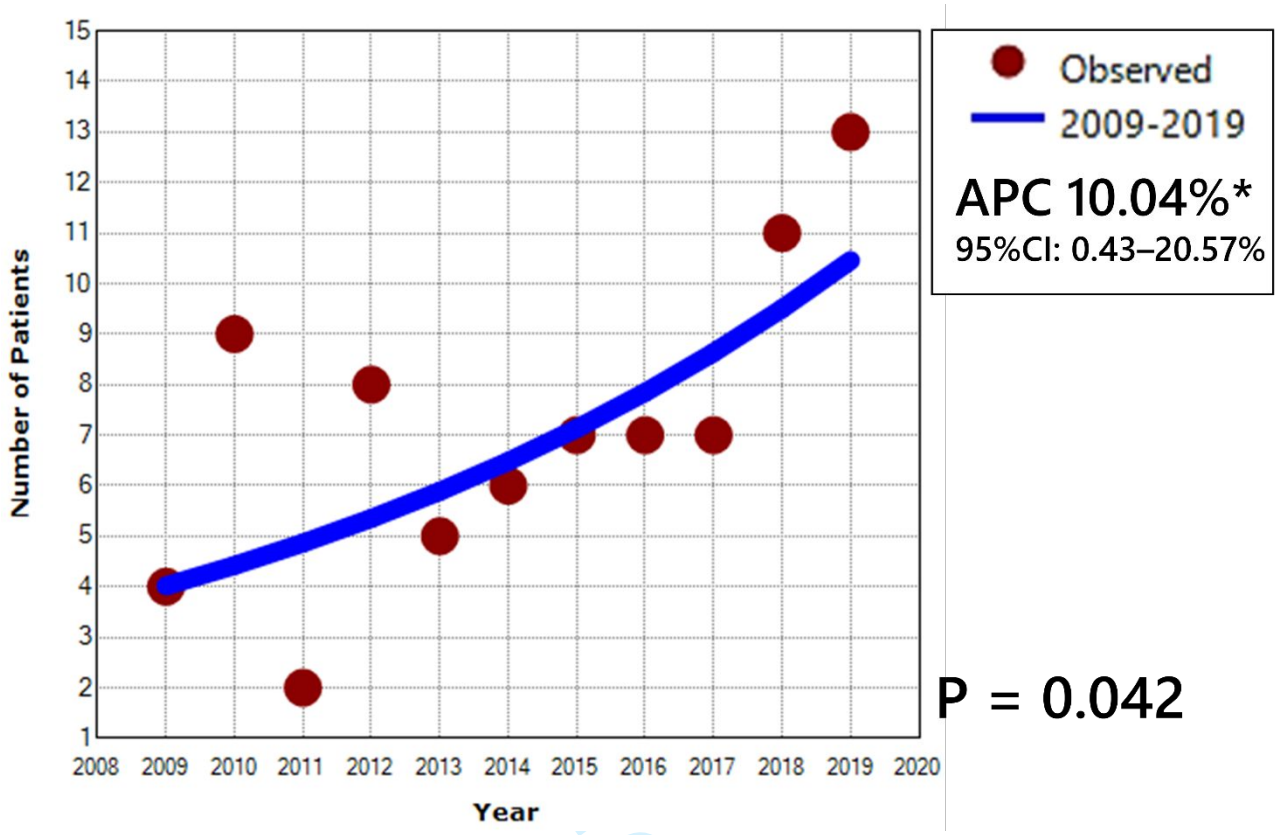


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	9.88*	1.39	19.09	2.65	0.026
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	9.88*	1.39	19.09	2.65	0.026
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

i. Trend Analysis for Total CRC Cases Originated from Descending Colon

1. Chart

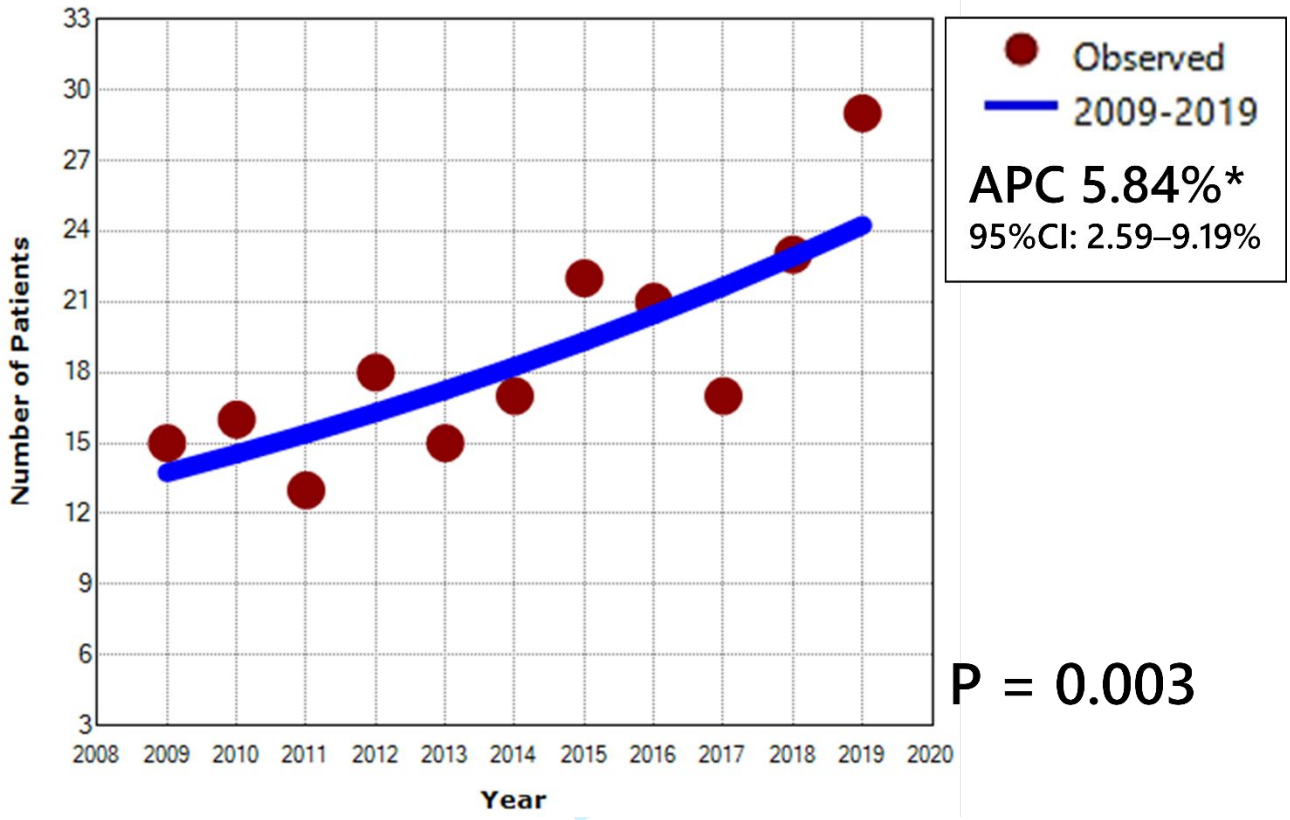


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	10.04*	0.43	20.57	2.37	0.042
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	10.04*	0.43	20.57	2.37	0.042
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

j. Trend Analysis for Total CRC Cases Originated from Sigmoid

1. Chart



2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

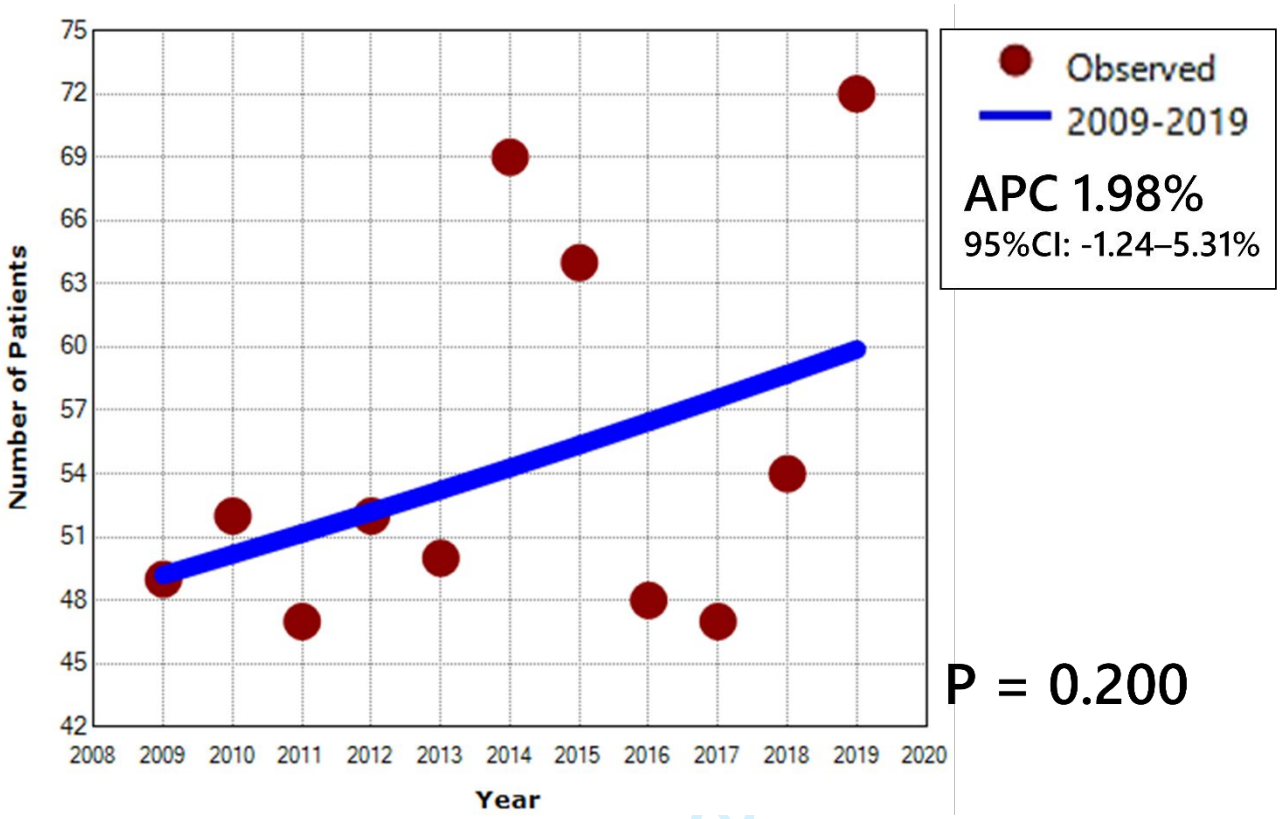
Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	5.84*	2.59	9.19	4.12	0.003
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	5.84*	2.59	9.19	4.12	0.003
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

Supplementary File 2.

Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement

a. Trend Analysis for CRC Cases Among Young Patients

1. Chart

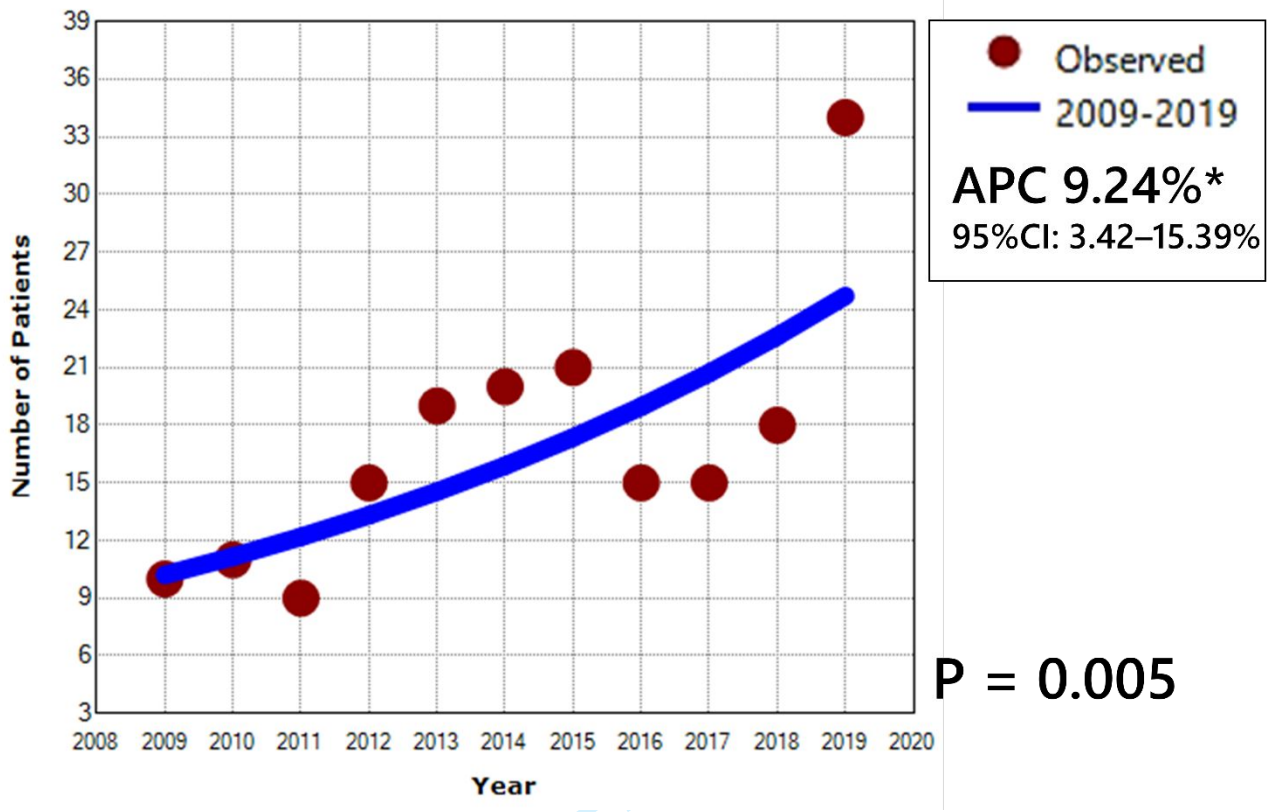


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.98	-1.24	5.31	1.38	0.200
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.98	-1.24	5.31	1.38	0.200
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Colon Cancer Cases Among Young Patients

1. Chart

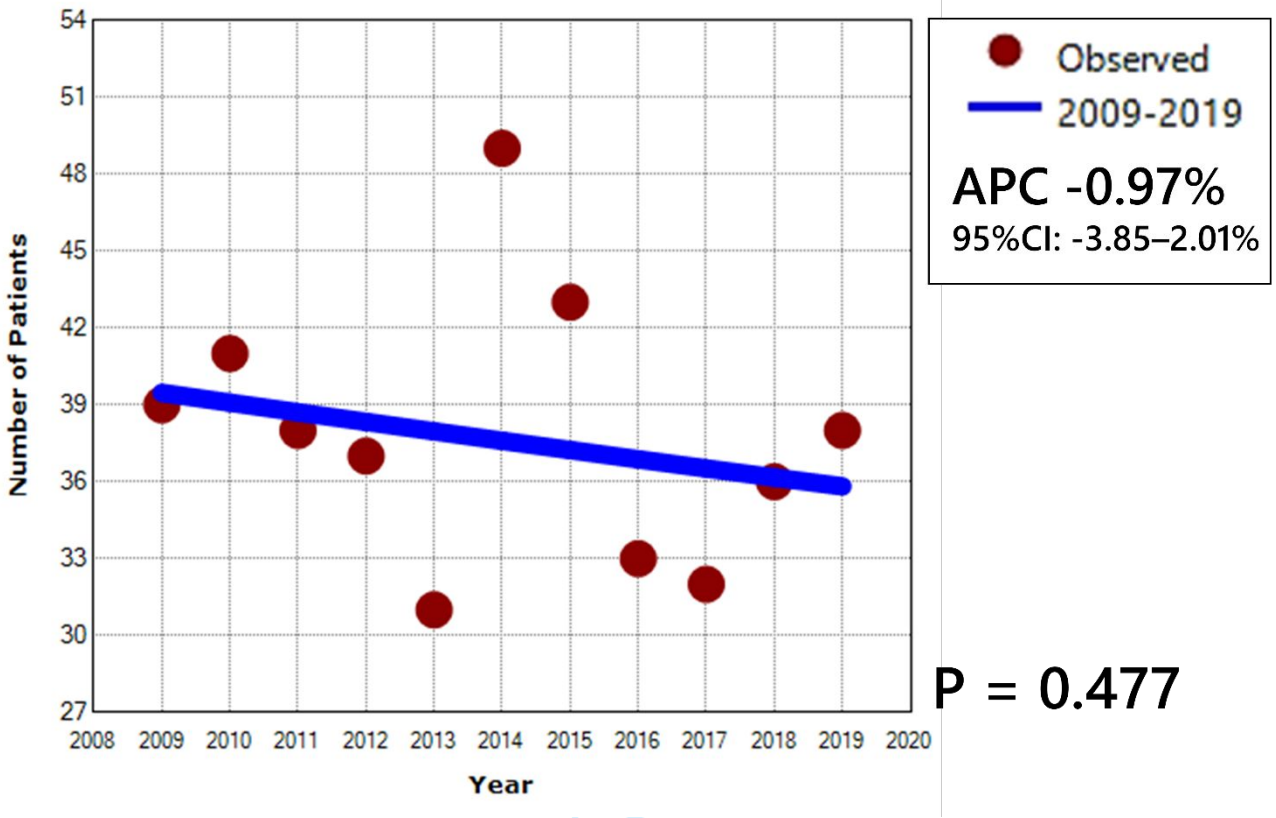


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	9.24*	3.42	15.39	3.65	0.005
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	9.24*	3.42	15.39	3.65	0.005
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Rectal Cancer Cases Among Young Patients

1. Chart

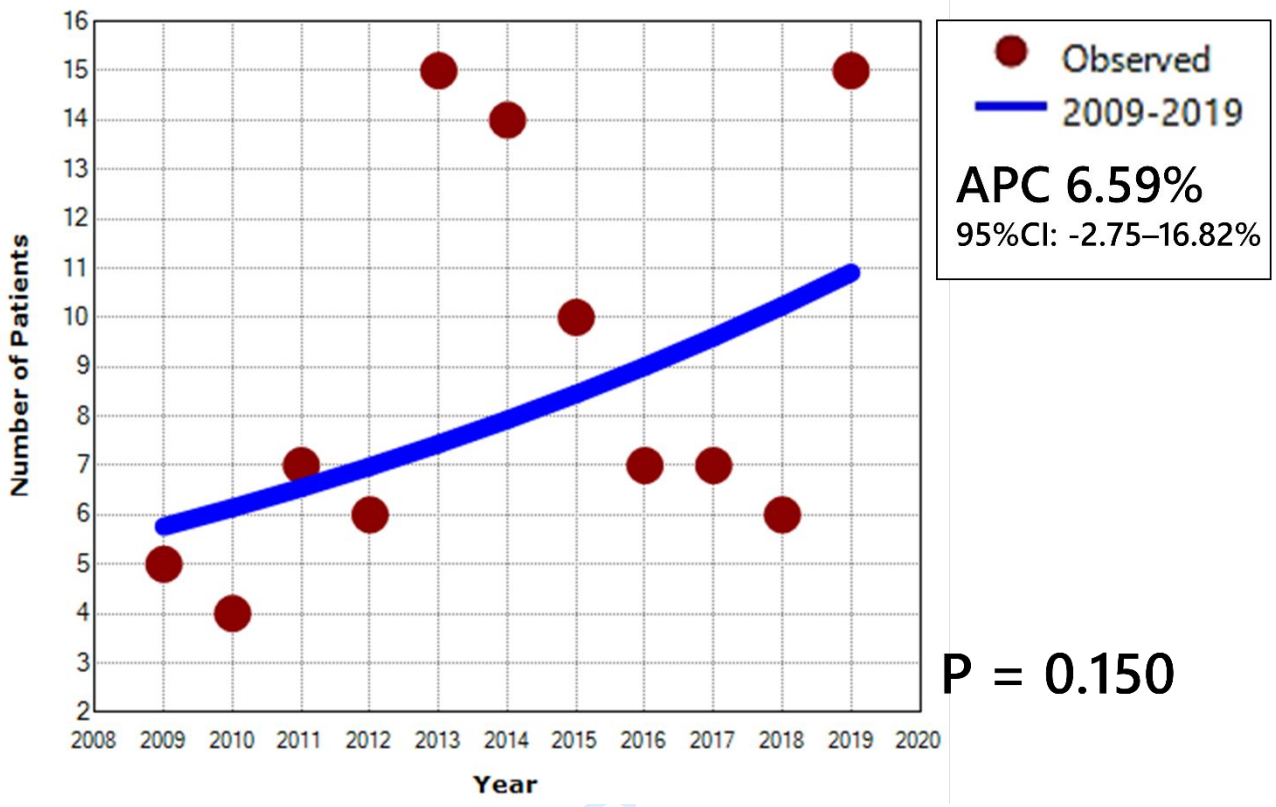


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.97	-3.85	2.01	-0.74	0.477
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.97	-3.85	2.01	-0.74	0.477
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Right-Sided CRC Cases Among Young Patients

1. Chart

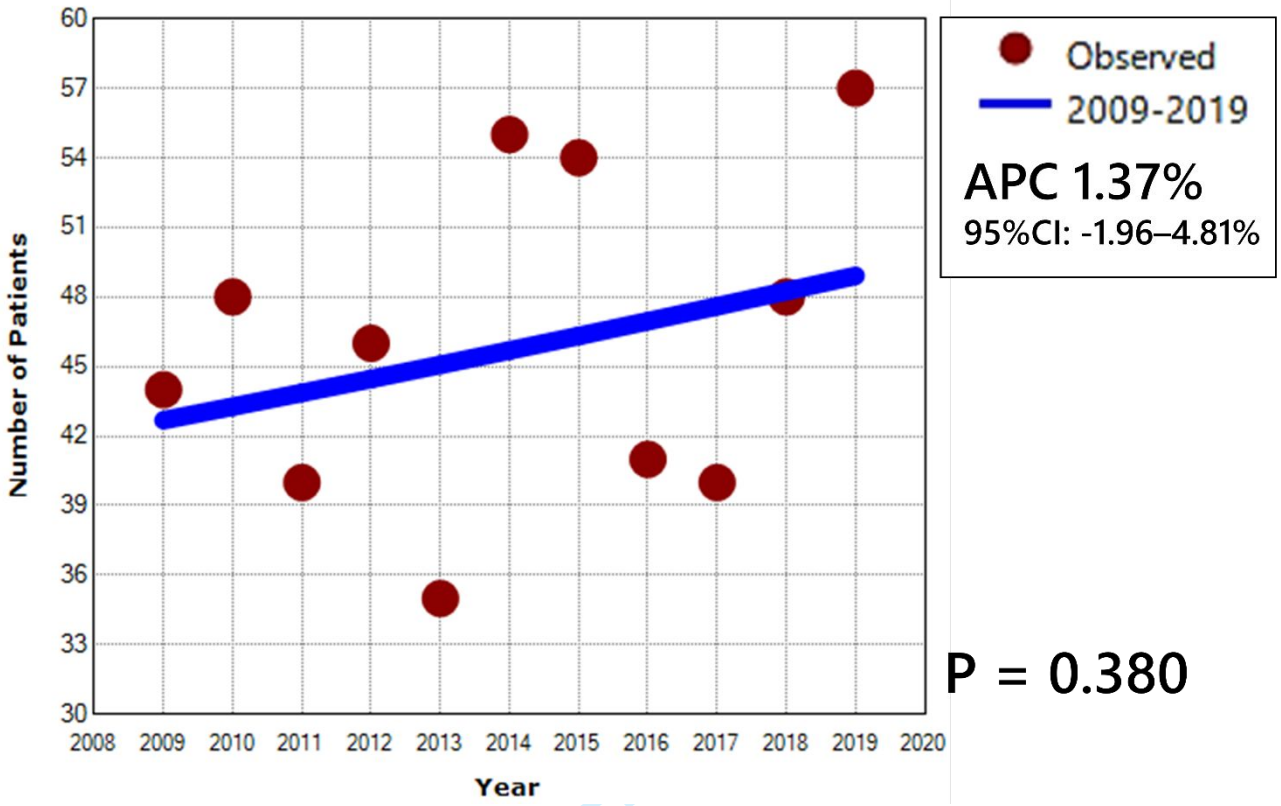


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.59	-2.75	16.82	1.57	0.150
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.59	-2.75	16.82	1.57	0.150
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Left-Sided CRC Cases Among Young Patients

1. Chart



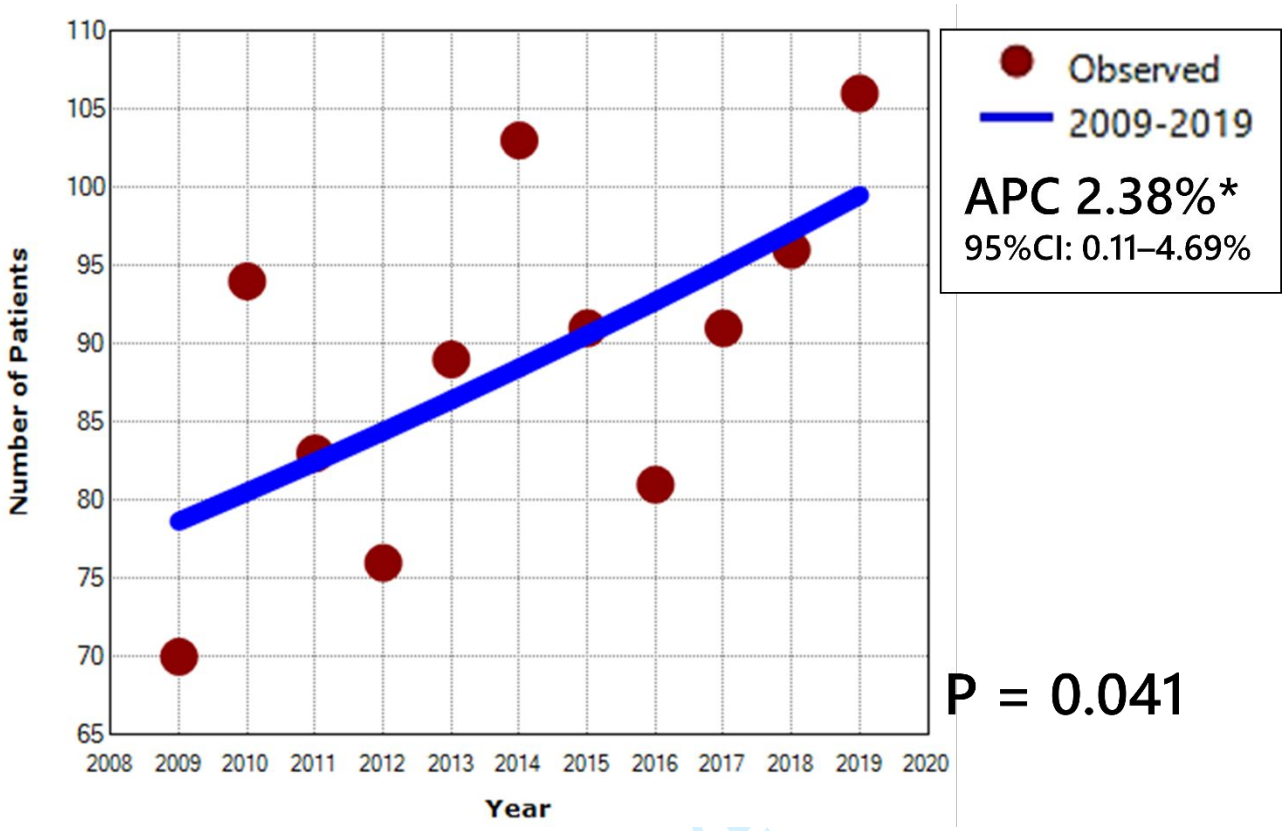
2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.37	-1.96	4.81	0.92	0.380
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.37	-1.96	4.81	0.92	0.380
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

Supplementary File 3.
Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among old patients based on tumor location and tumor side involvement

a. Trend Analysis for CRC Cases Among Old Patients

1. Chart

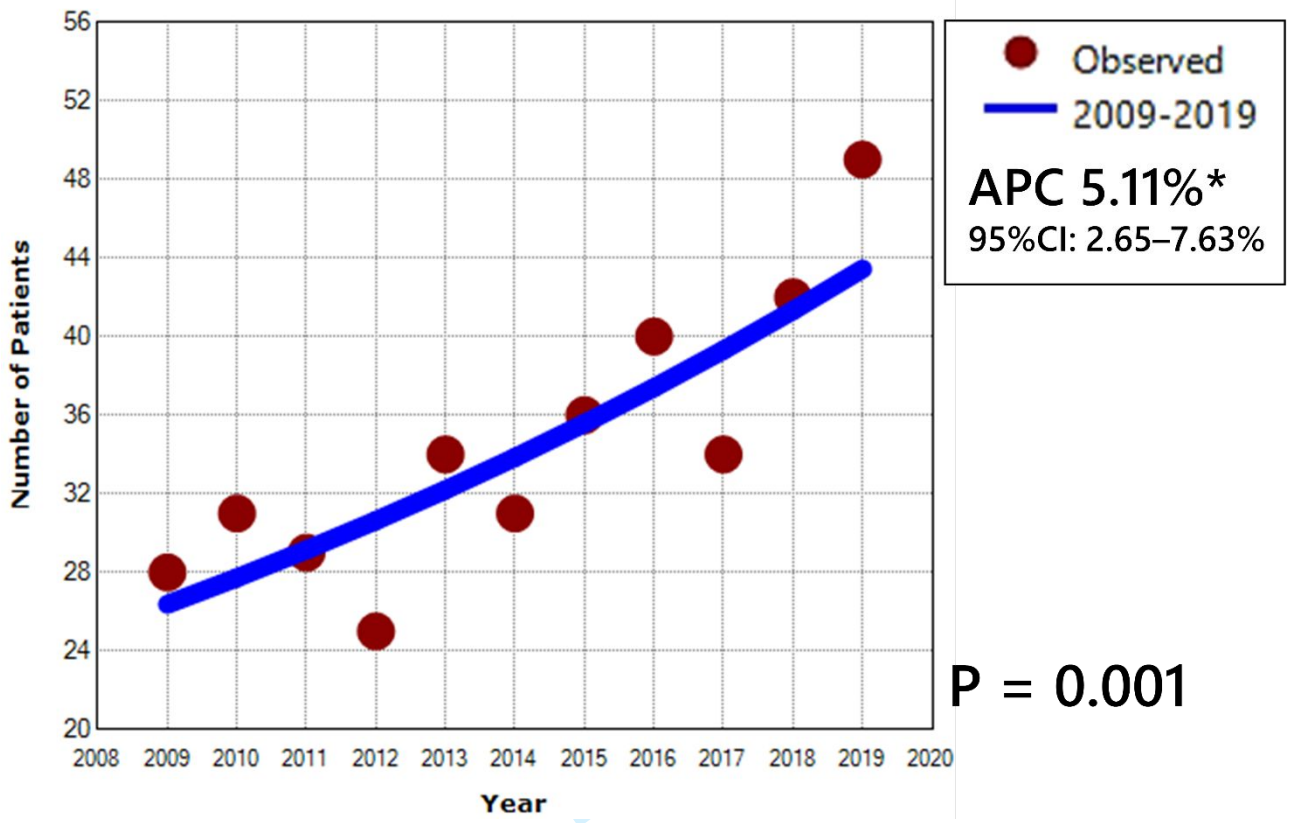


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	2.38*	0.11	4.69	2.38	0.041
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	2.38*	0.11	4.69	2.38	0.041
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Colon Cancer Cases Among Old Patients

1. Chart

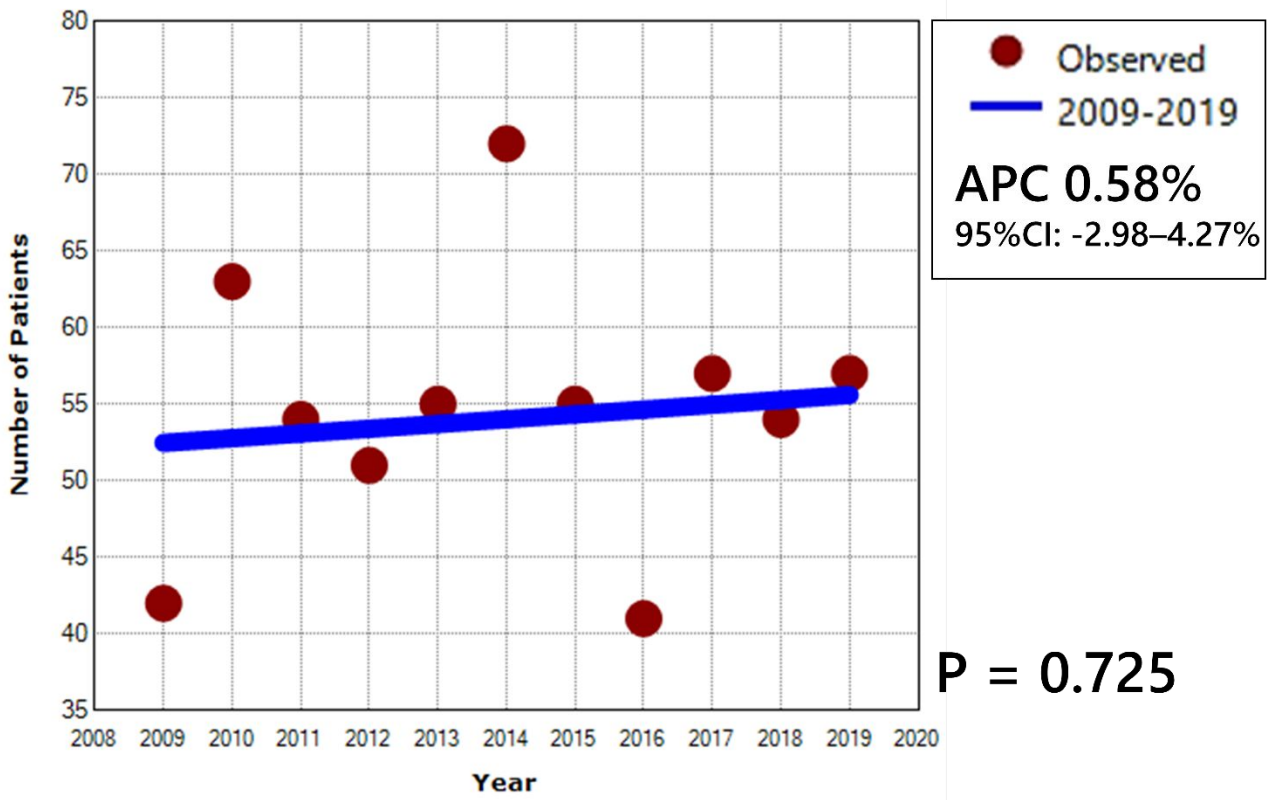


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	5.11*	2.65	7.63	4.76	0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	5.11*	2.65	7.63	4.76	0.001
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Rectal Cancer Cases Among Old Patients

1. Chart

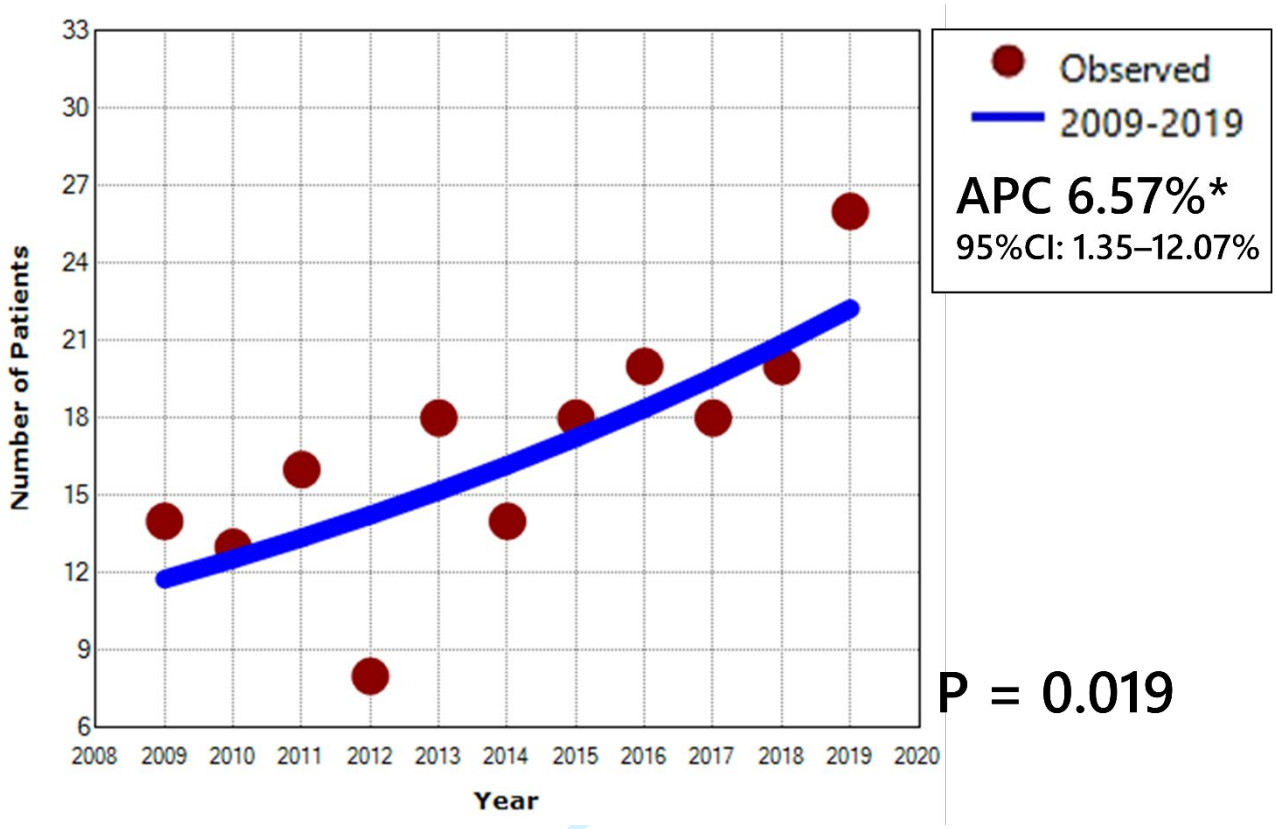


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	0.58	-2.98	4.27	0.36	0.725
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	0.58	-2.98	4.27	0.36	0.725
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Right-Sided CRC Cases Among Old Patients

1. Chart

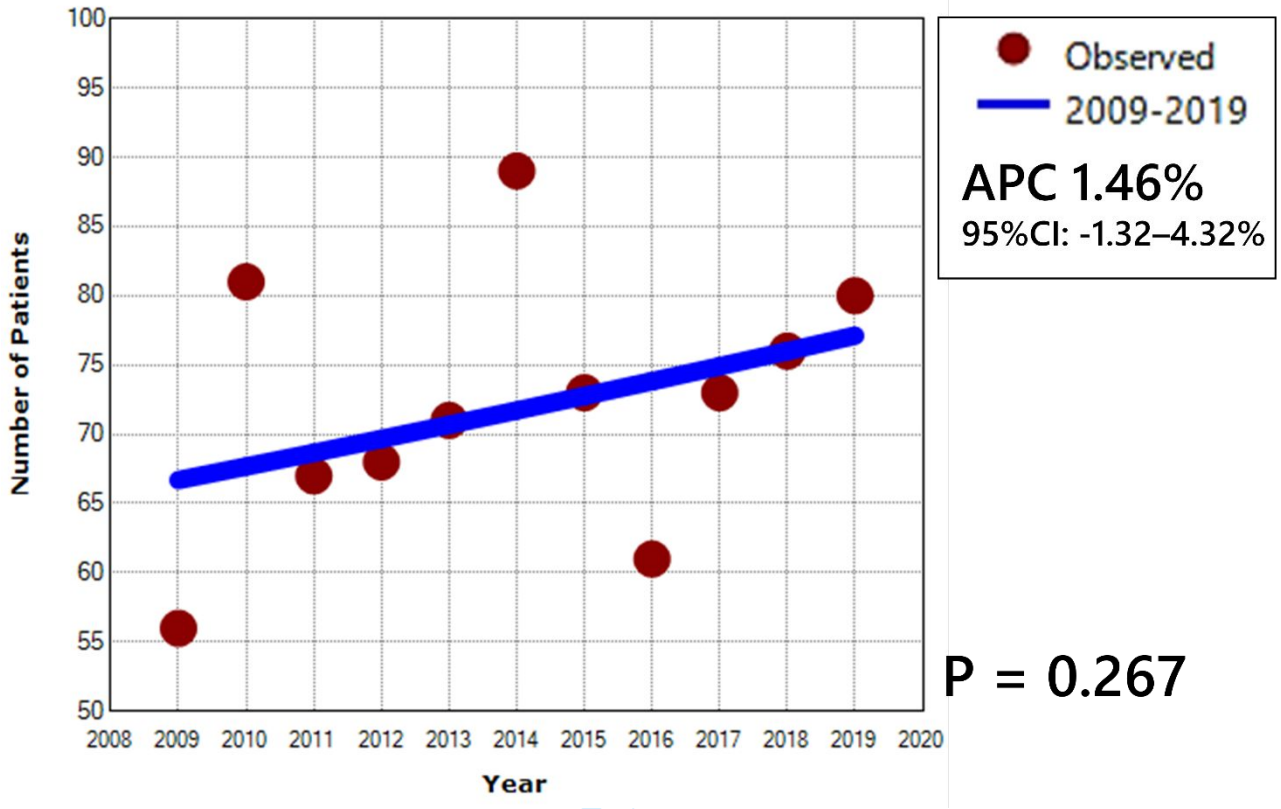


2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.57*	1.35	12.07	2.87	0.019
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.57*	1.35	12.07	2.87	0.019
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Left-Sided CRC Cases Among Old Patients

1. Chart



2. Significance test uses a Monte Carlo permutation method to determine the best fit line(s) for analysis of the time series:

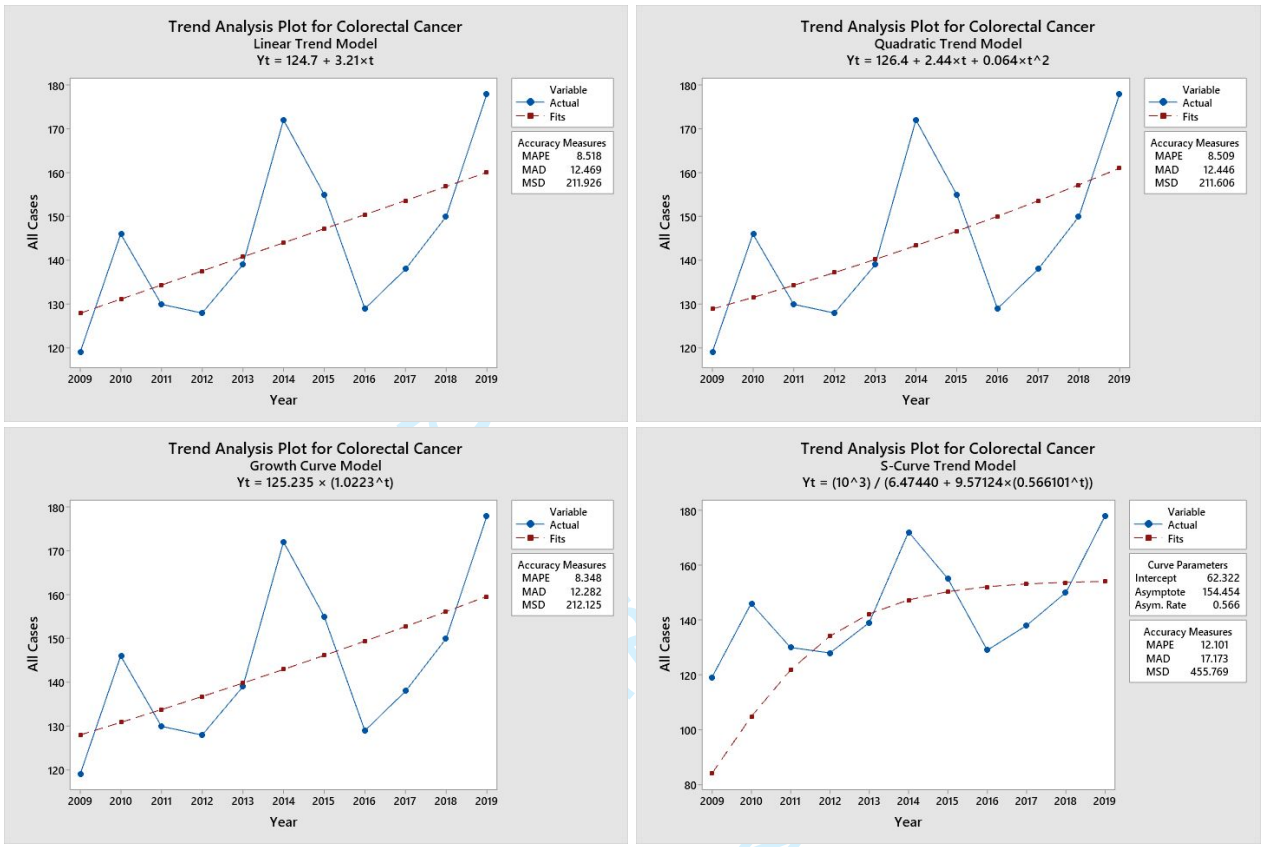
Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.46	-1.32	4.32	1.18	0.267
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.46	-1.32	4.32	1.18	0.267
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

Supplementary File 4.

Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among all patients based on tumor location and tumor side involvement

a. Regression Model for Total CRC Cases

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 124.7 + 3.21t$	8.518	12.469	211.926
Quadratic	$Yt = 126.4 + 2.44t + 0.064t^2$	8.509	12.446	**211.606**
Exponential Growth*	**$Yt = 125.235 \times (1.0223^t)$**	**8.348**	**12.282**	212.125
S-shaped	$Yt = 10^3 / (6.4744 + 9.5712 \times (0.5661^t))$	12.101	17.173	455.769

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.053	1	.053	4.558	.062
Residual	.106	9	.012		
Total	.159	10			

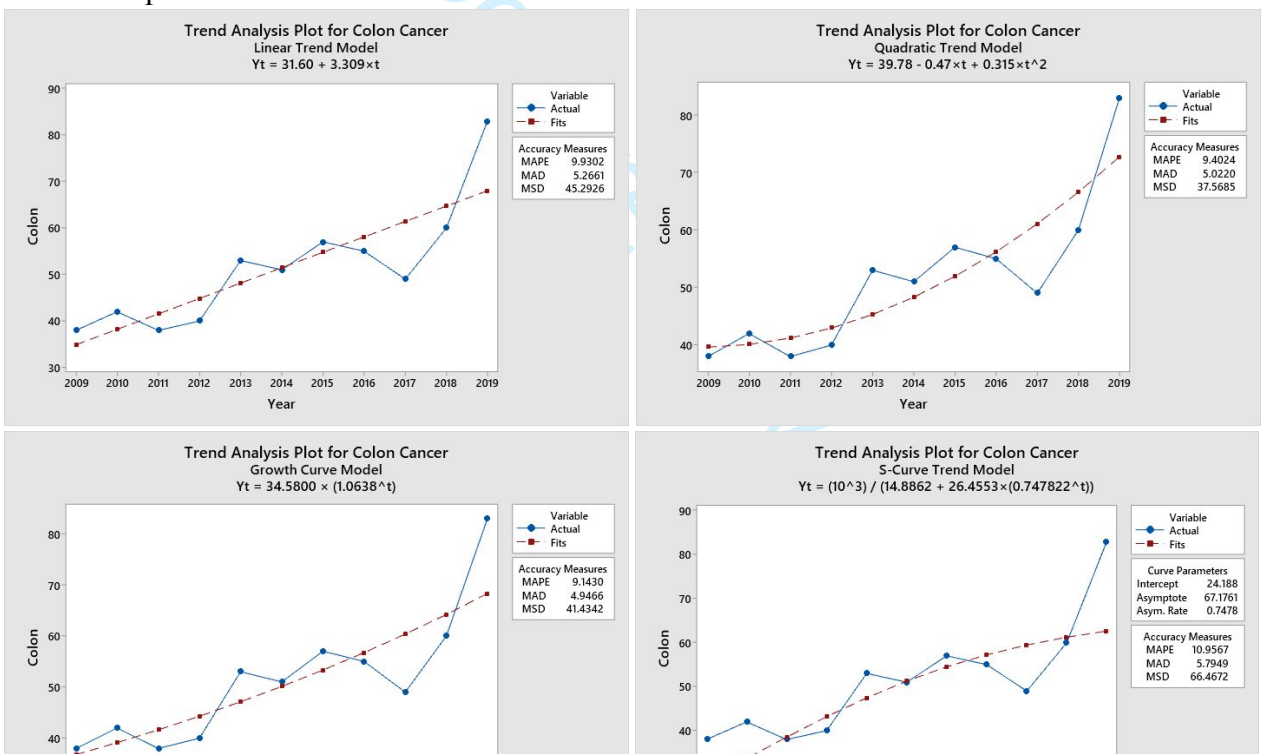
The independent variable is Year.

3. Forecasting following ten-year cases using Exponential growth curve model.

Period	Forecast
2020	163.163
2021	166.800
2022	170.518
2023	174.319
2024	178.205
2025	182.177
2026	186.238
2027	190.389
2028	194.633
2029	198.972
Mean	180.541
Total	1,805.41

b. Regression Model for Total Colon Cancer Cases

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 31.60 + 3.309t$	9.9302	5.2661	45.2926
Quadratic	$Yt = 39.78 - 0.47t + 0.315t^2$	9.4024	5.0220	**37.5685**
Exponential Growth*	**$Yt = 34.58 \times (1.0638^t)$**	**9.1430**	**4.9466**	41.4342
S-shaped	$Yt = 10^3 / (14.8862 + 26.4553 \times (0.747822^t))$	10.9567	5.7949	66.4672

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.421	1	.421	29.084	**.000**
Residual	.130	9	.014		
Total	.551	10			

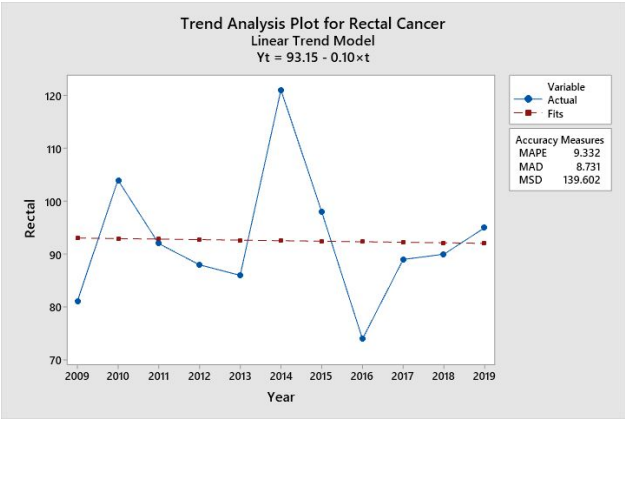
The independent variable is Year.

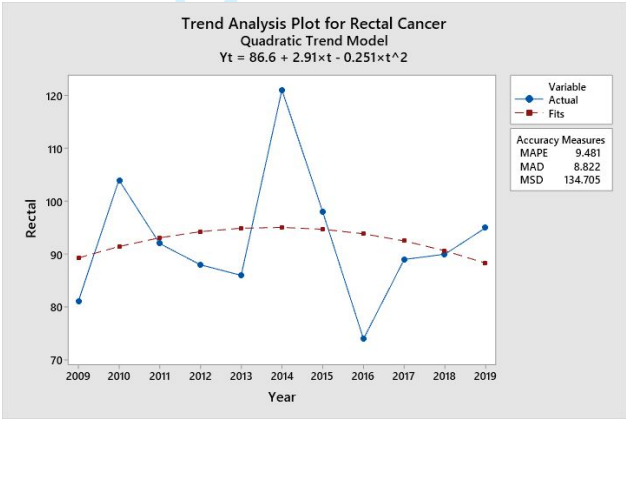
3. Forecasting following ten-year cases using Exponential growth curve model.

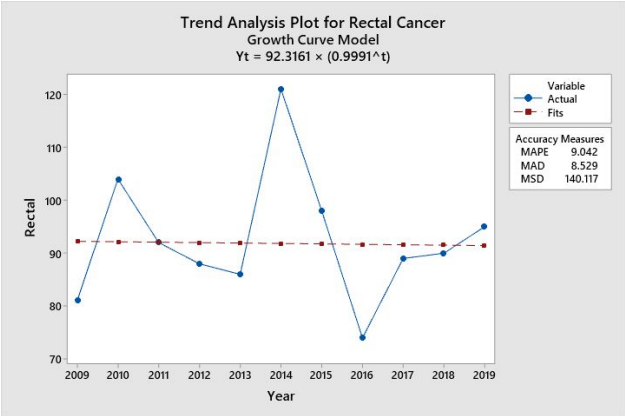
Period	Forecast
2020	72.652
2021	77.288
2022	82.221
2023	87.468
2024	93.051
2025	98.989
2026	105.307
2027	112.027
2028	119.177
2029	126.783
Mean	97.4963
Total	974.963

c. Regression Model for Total Rectal Cancer Cases

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 93.15 - 0.10t$	9.332	8.731	139.602
Quadratic	$Yt = 86.6 + 2.91t + 0.25t^2$	9.481	8.822	**134.705**
Exponential Growth*	**$Yt = 92.3161 \times (0.9991^t)$**	**9.042**	**8.529**	140.117
S-shaped	*Error: Can not fit model to these data*	*n/a*	*n/a*	*n/a*

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.000	1	.000	.005	.948
Residual	.167	9	.019		
Total	.167	10			

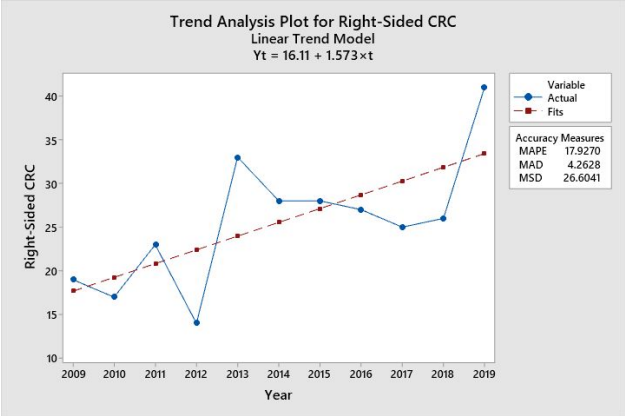
The independent variable is Year.

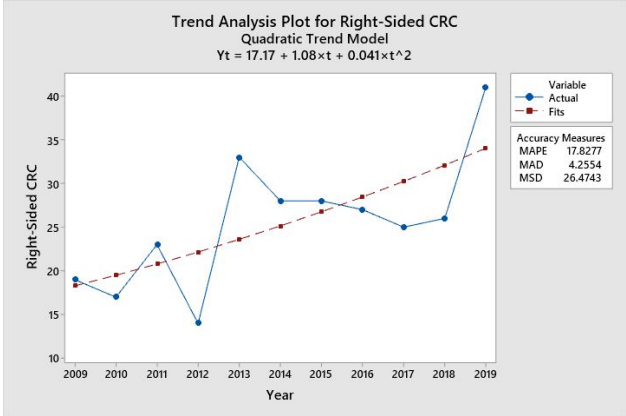
3. Forecasting following ten-year cases using Exponential growth curve model.

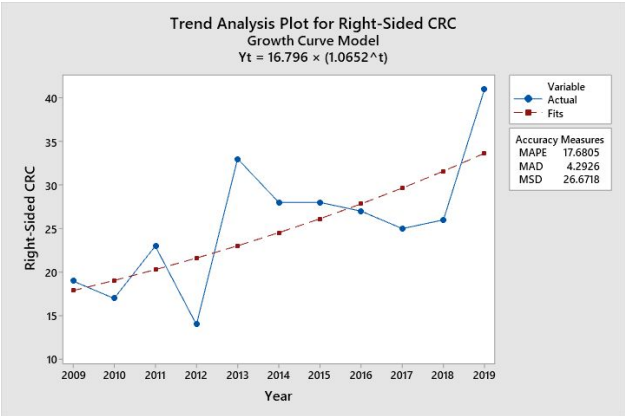
Period	**Forecast**
2020	91.3487
2021	91.2685
2022	91.1884
2023	91.1084
2024	91.0284
2025	90.9486
2026	90.8688
2027	90.7890
2028	90.7094
2029	90.6298
Mean	90.9888
Total	909.888

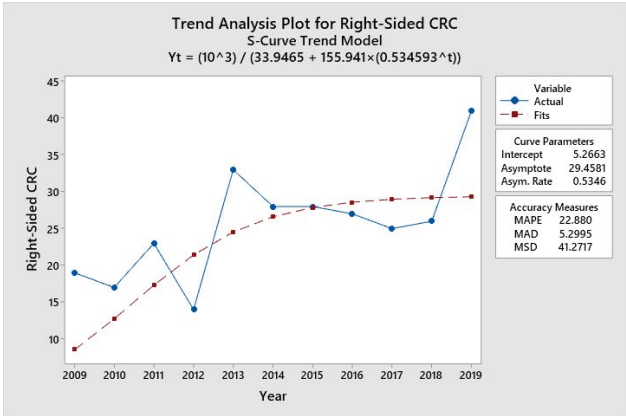
d. Regression Model for Total Right-Sided CRC Cases

1. Curve Options









Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 16.11 + 1.573t	17.927	4.2628	26.6041
Quadratic*	**$Yt = 17.17 + 1.08t + 0.041t^2$**	17.8277	**4.2554**	**26.4743**
Exponential Growth	$Yt = 16.796 \times (1.0652^t)$	**17.6805**	4.2926	26.6718
S-shaped	$Yt = 10^3 / (33.9465 + 155.941 \times (0.534593^t))$	22.8801	5.2995	41.2717

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Quadratic model) using ANOVA test in SPSS

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	272.109	1	272.109	8.369	**.018**
Residual	292.618	9	32.513		
Total	564.727	10			

The independent variable is Year.

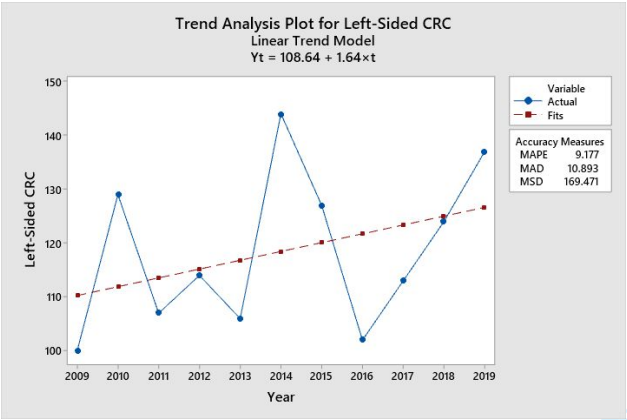
3. Forecasting following ten-year cases using Quadratic curve model.

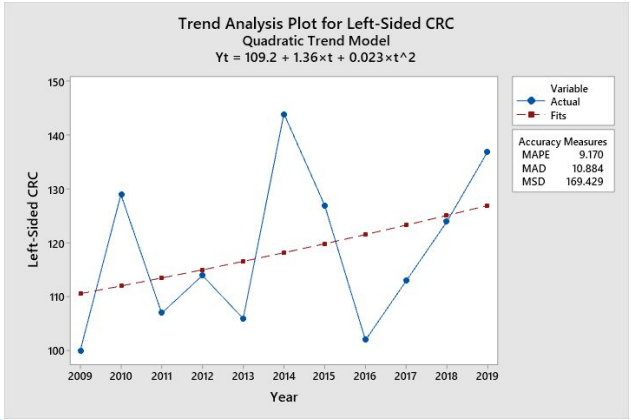
Period	Forecast
2020	36.0424
2021	38.1455
2022	40.3301
2023	42.5963

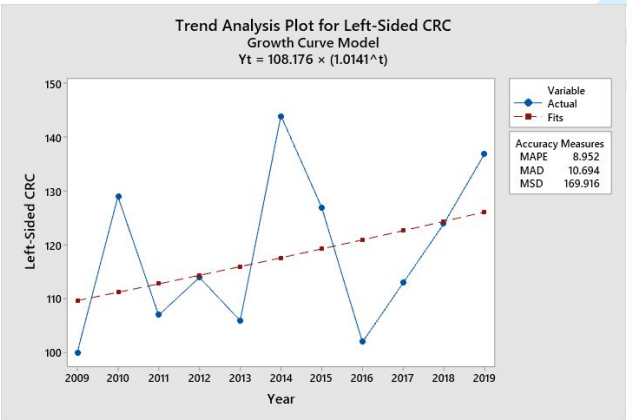
2024	44.9441
2025	47.3734
2026	49.8844
2027	52.4769
2028	55.1510
2029	57.9068
Mean	46.48509
Total	464.8509

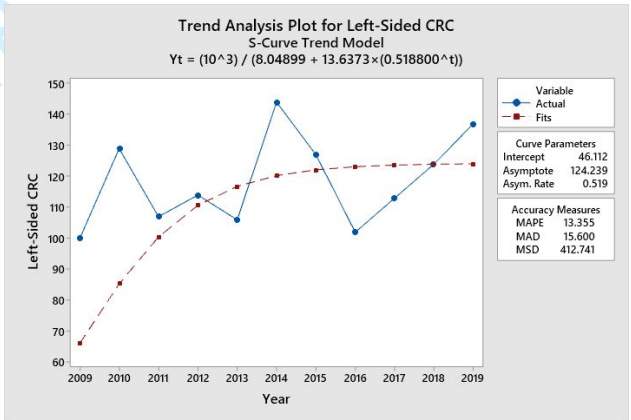
e. Regression Model for Total Left-Sided CRC Cases

1. Curve Options









Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 108.64 + 1.64t$	9.177	10.893	169.471
Quadratic	$Yt = 109.2 + 1.36t + 0.023t^2$	9.170	10.884	**169.429**
Exponential Growth*	**$Yt = 108.176 \times (1.0141^t)$**	**8.952**	**10.694**	169.916
S-shaped	$Yt = 10^3 / (8.04899 + 13.6373 \times (0.518800^t))$	13.355	15.600	412.741

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.

Regression	.022	1	.022	1.501	.252
Residual	.129	9	.014		
Total	.150	10			

The independent variable is Year.

3. Forecasting following ten-year cases using Exponential growth curve model.

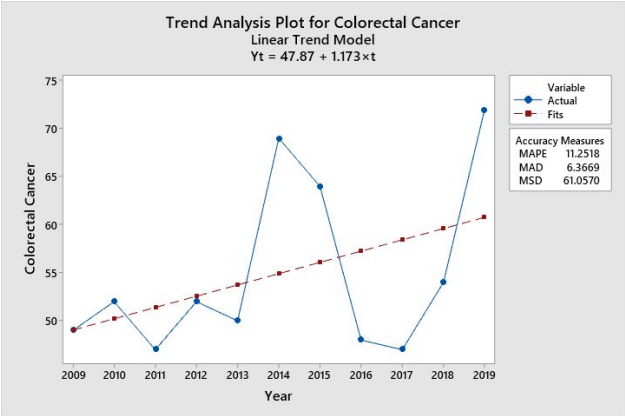
Period	Forecast
2020	127.936
2021	129.737
2022	131.564
2023	133.416
2024	135.294
2025	137.199
2026	139.131
2027	141.090
2028	143.076
2029	145.090
Mean	136.3533
Total	1363.533

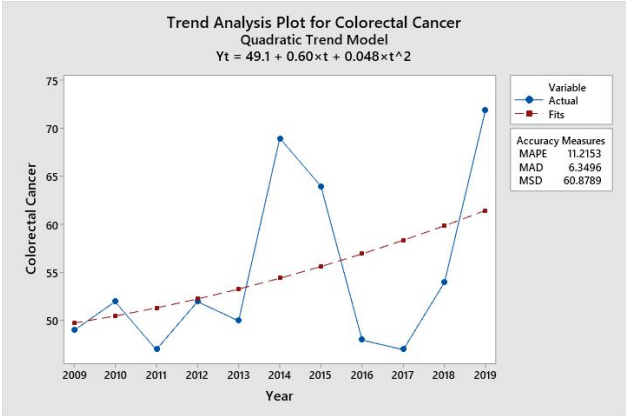
Supplementary File 5.

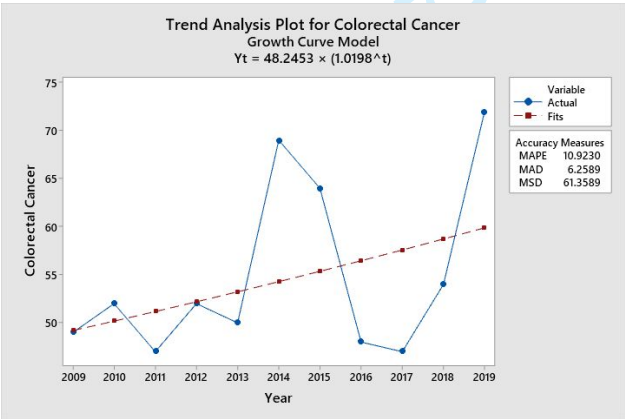
Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among young patients based on tumor location and tumor side involvement

a. Regression Model for CRC Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 47.87 + 1.173t$	11.2518	6.3669	61.0570
Quadratic	$Yt = 49.1 + 0.60t + 0.049t^2$	11.2153	6.3496	**60.8789**
Exponential Growth*	**$Yt = 48.2453 \times (1.0198^t)$**	**10.9230**	**6.2589**	61.3589
S-shaped	*Error: Can not fit model to these data*	*n/a*	*n/a*	*n/a*

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.042	1	.042	1.916	.200
Residual	.200	9	.022		
Total	.242	10			

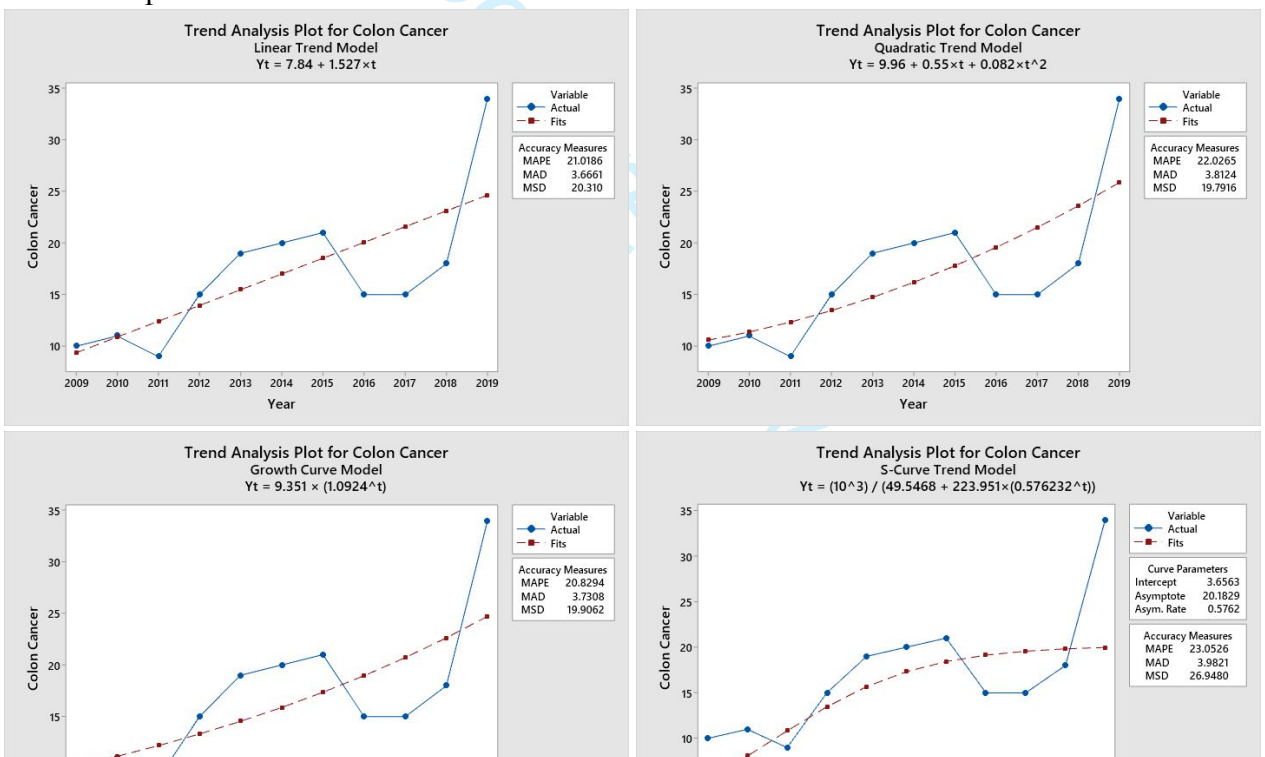
The independent variable is Year.

3. Forecasting following ten-year cases using Exponential growth curve model.

Period	Forecast
2020	61.0779
2021	62.2902
2022	63.5266
2023	64.7875
2024	66.0734
2025	67.3849
2026	68.7224
2027	70.0864
2028	71.4776
2029	72.8963
Mean	66.83232
Total	668.3232

b. Regression Model for Colon Cancer Cases Among Young Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 7.84 + 1.527t$	21.0186	3.6661	20.3107
Quadratic	$Yt = 9.96 + 0.55t + 0.082t^2$	22.0265	3.8124	**19.7916**
Exponential Growth*	**$Yt = 9.351\times (1.0924^t)$**	**20.8294**	**3.7308**	19.9062
S-shaped	$Yt = 10^3 / (49.5468 + (223.951 \times 0.576232^t))$	23.0526	3.9821	26.9480

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.859	1	.859	13.320	**.005**
Residual	.581	9	.065		
Total	1.440	10			

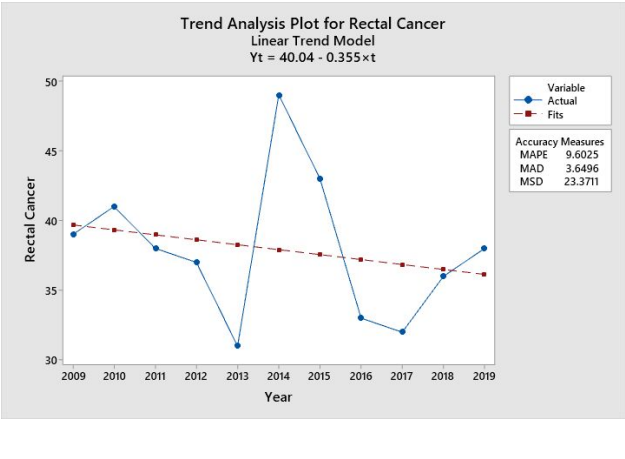
The independent variable is Year.

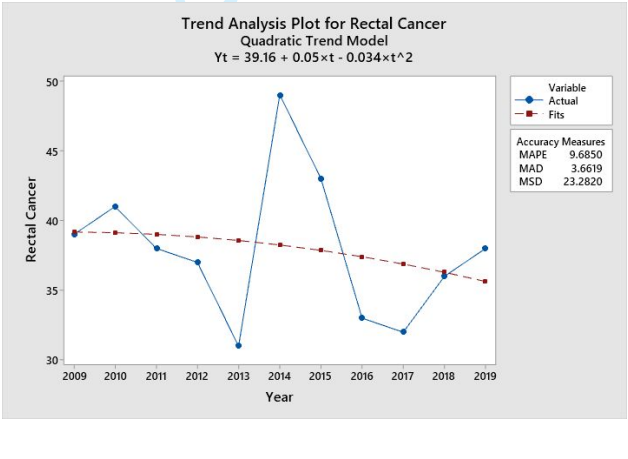
3. Forecasting following ten-year cases using Exponential growth curve model.

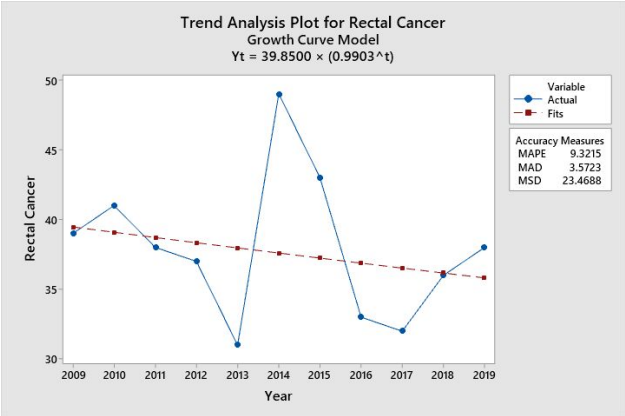
Period	Forecast
2020	27.0046
2021	29.4998
2022	32.2256
2023	35.2031
2024	38.4559
2025	42.0091
2026	45.8907
2027	50.1310
2028	54.7630
2029	59.8230
Mean	41.50058
Total	415.0058

c. Regression Model for Rectal Cancer Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 40.04 - 0.355t$	9.6025	3.6496	23.3711
Quadratic	$Yt = 39.16 + 0.05t - 0.034t^2$	9.6850	3.6619	**23.2820**
Exponential Growth*	**$Yt = 39.85 \times (0.9903^t)$**	**9.3215**	**3.5723**	23.4688
S-shaped	*Error: Can not fit model to these data*	*n/a*	*n/a*	*n/a*

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.010	1	.010	.551	.477
Residual	.169	9	.019		
Total	.180	10			

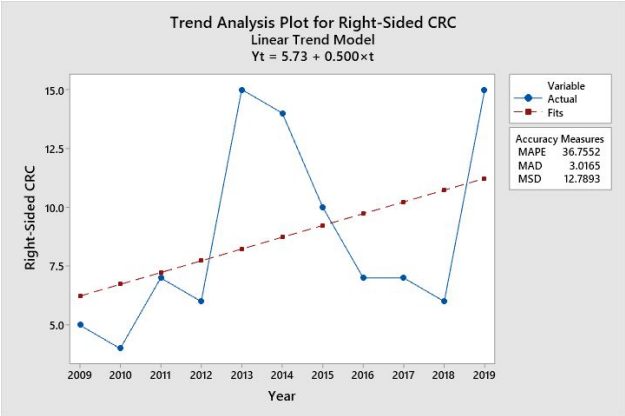
The independent variable is Year.

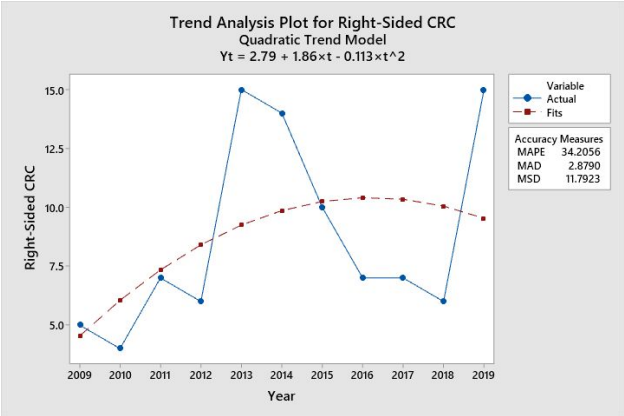
3. Forecasting following ten-year cases using Exponential growth curve model.

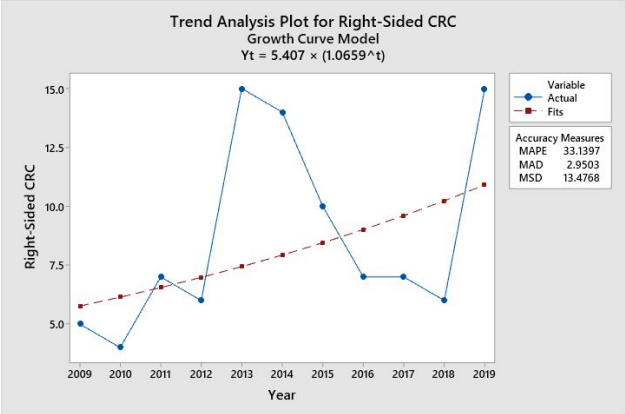
Period	Forecast
2020	35.4703
2021	35.1278
2022	34.7886
2023	34.4527
2024	34.1201
2025	33.7906
2026	33.4644
2027	33.1413
2028	32.8213
2029	32.5044
Mean	33.96815
Total	339.6815

d. Regression Model for Right-Sided CRC Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 5.73 + 0.5t	36.7552	3.0165	12.7893
Quadratic*	**$Yt = 2.79 + 1.86t - 0.113t^2$**	34.2056	**2.8790**	**11.7923**
Exponential Growth	$Yt = 5.407 \times (1.0659^t)$	**33.1397**	2.9503	13.4768
S-shaped	*Error: Can not fit model to these data*	*n/a*	*n/a*	*n/a*

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Quadratic curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	27.500	1	27.500	1.759	.217
Residual	140.682	9	15.631		
Total	168.182	10			

The independent variable is Year.

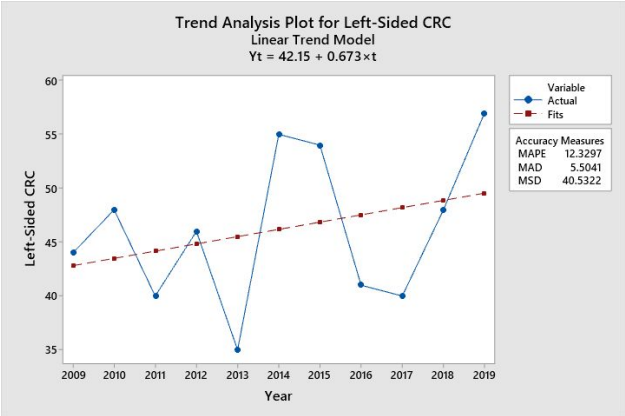
3. Forecasting following ten-year cases using Quadratic curve model.

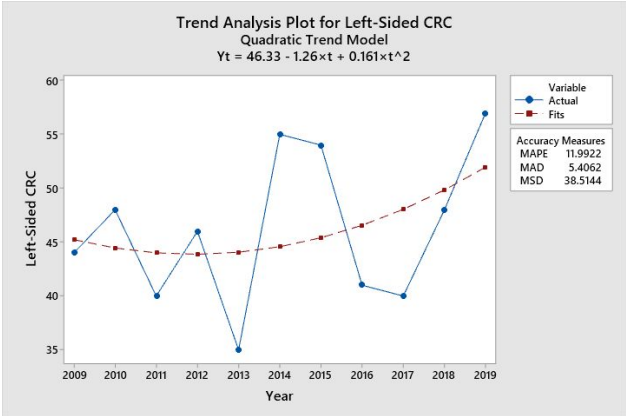
Period	Forecast
2020	8.78788
2021	7.81818
2022	6.62238
2023	5.20047
2024	3.55245

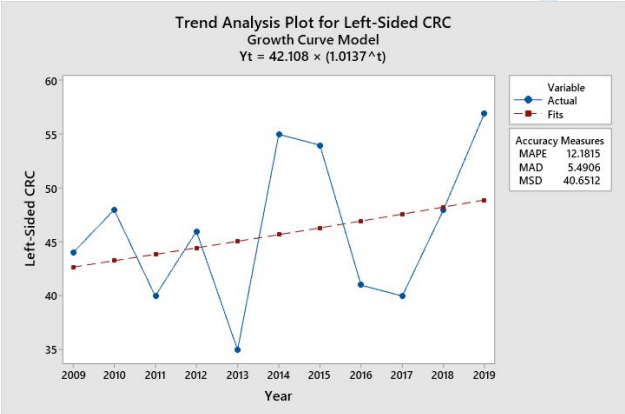
2025	1.67832
2026	-0.42191
2027	-2.74825
2028	-5.30070
2029	-8.07925
Mean	1.710957
Total	17.10957

e. Regression Model for Left-Sided CRC Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 42.15 + 0.673t	12.3297	5.5041	40.5322
Quadratic*	**$Yt = 46.33 - 1.26t + 0.161t^2$**	**11.9922**	**5.4062**	**38.5144**
Exponential Growth	$Yt = 42.108 \times (1.0137^t)$	12.1815	5.4906	40.6512
S-shaped	*Error: Can not fit model to these data*	*n/a*	*n/a*	*n/a*

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Exponential growth curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	49.828	1	49.828	1.006	.342
Residual	445.808	9	49.534		

Total	495.636	10			

The independent variable is Year.

3. Forecasting following ten-year cases using Exponential growth curve model.

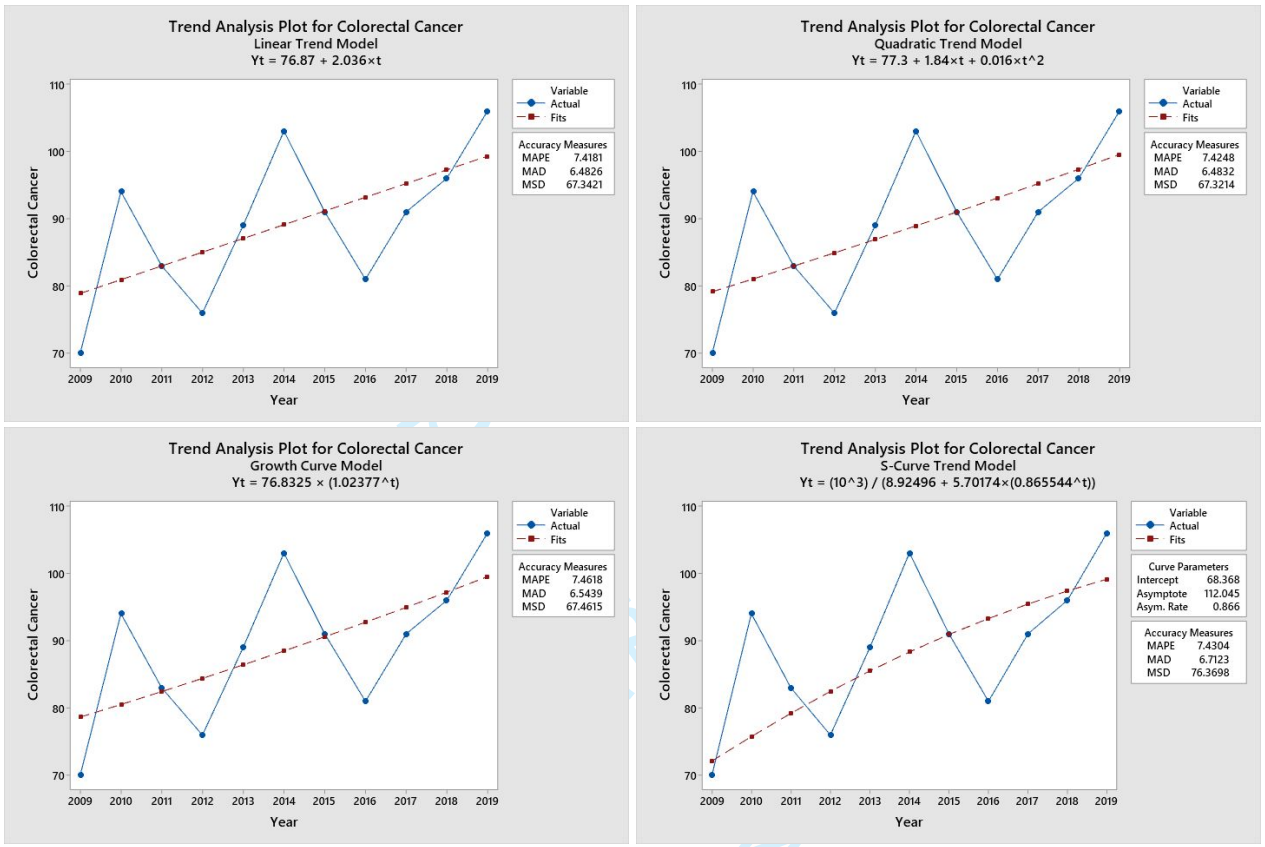
Period	Forecast
2020	54.4000
2021	57.1636
2022	60.2490
2023	63.6559
2024	67.3846
2025	71.4350
2026	75.8070
2027	80.5007
2028	85.5161
2029	90.8531
Mean	70.6965
Total	706.965

Supplementary File 6.

Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among old patients based on tumor location and tumor side involvement

a. Regression Model for CRC Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 76.87 + 2.036t	7.4181	**6.4826**	67.3421
Quadratic*	**$Yt = 77.3 + 1.84t + 0.016t^2$**	**7.4248**	6.4832	**67.3214**
Exponential Growth	$Yt = 76.8325 \times (1.02377^t)$	7.4618	6.5439	67.4615
S-shaped	$Yt = 10^3 / (8.92496 + 5.70174 \times (0.865544^t))$	7.4304	6.7123	76.3698

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Quadratic curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	456.159	1	456.159	5.542	**.043**
Residual	740.750	9	82.306		
Total	1196.909	10			

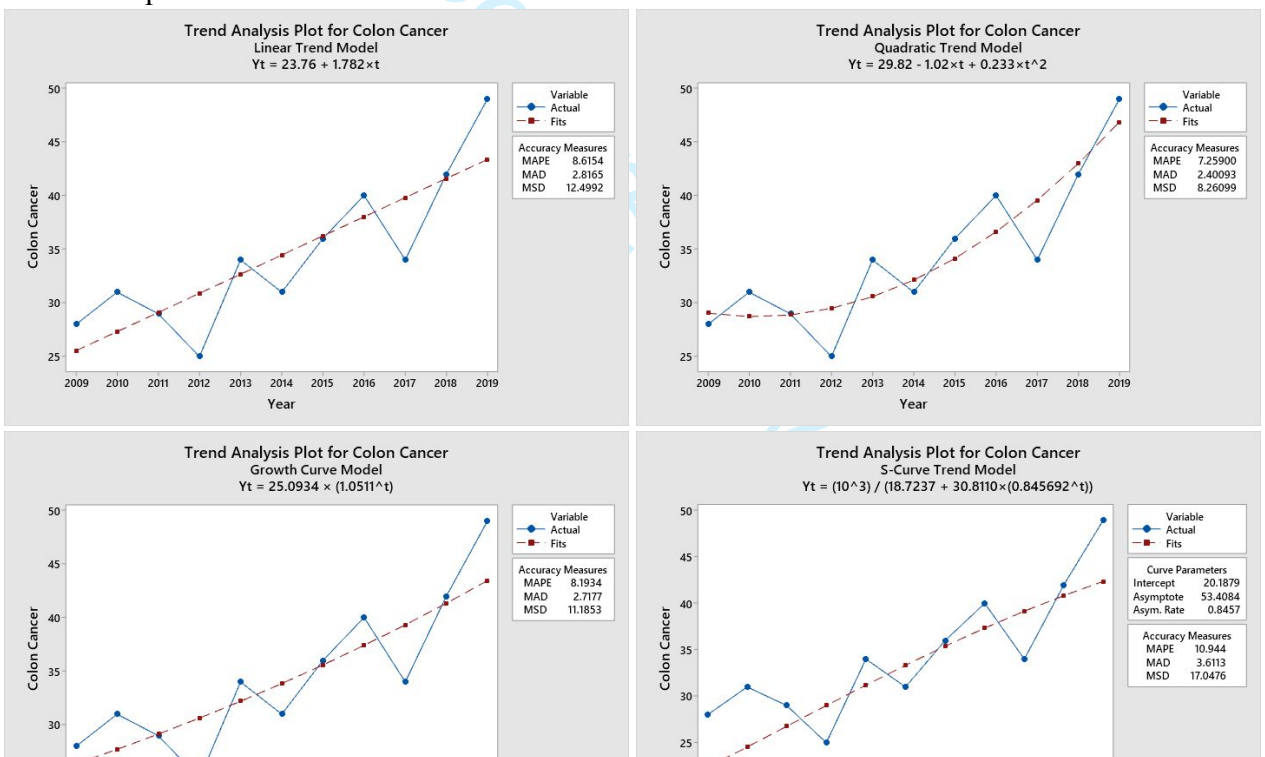
The independent variable is Year.

3. Forecasting following ten-year cases using Quadratic curve model.

Period	Forecast
2020	101.733
2021	103.982
2022	106.263
2023	108.577
2024	110.923
2025	113.302
2026	115.714
2027	118.158
2028	120.635
2029	123.145
Mean	112.2432
Total	1122.432

b. Regression Model for Colon Cancer Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 23.76 + 1.782t$	8.6154	2.8165	12.4992
Quadratic*	$\mathbf{Yt = 29.82 - 1.02t + 0.233t^2}$	**7.2590**	**2.40093**	**8.26099**
Exponential Growth	$Yt = 25.0934 \times (1.0511^t)$	8.1934	2.7177	11.1853
S-shaped	$Yt = 10^3 / (18.7237 + (30.8110 \times 0.845692^t))$	10.9444	3.6113	17.0476

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Quadratic curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	349.413	1	349.413	22.902	**.001**
Residual	137.314	9	15.257		
Total	486.727	10			

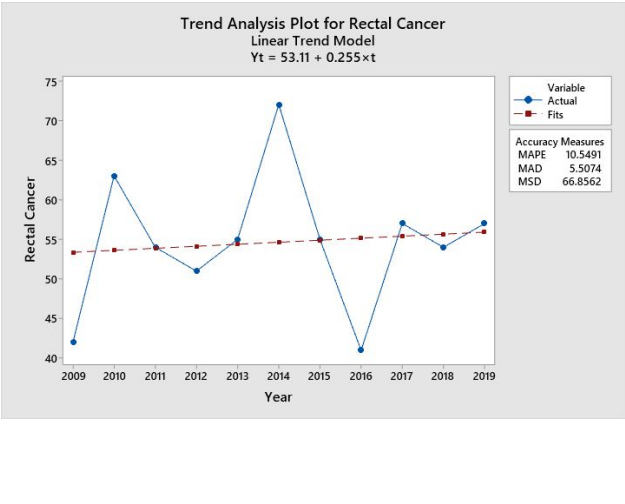
The independent variable is Year.

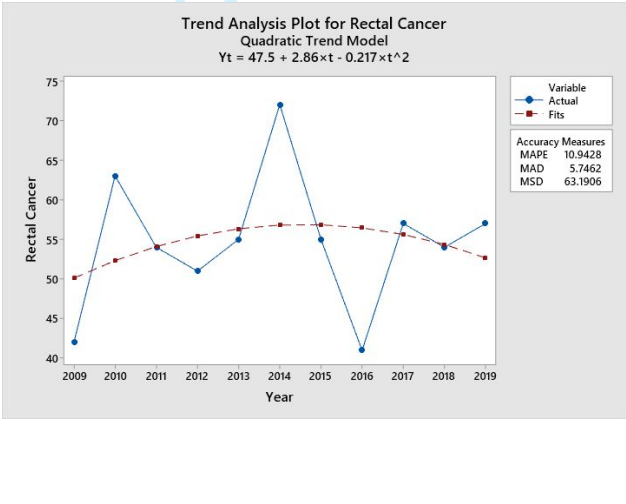
3. Forecasting following ten-year cases using Quadratic curve model.

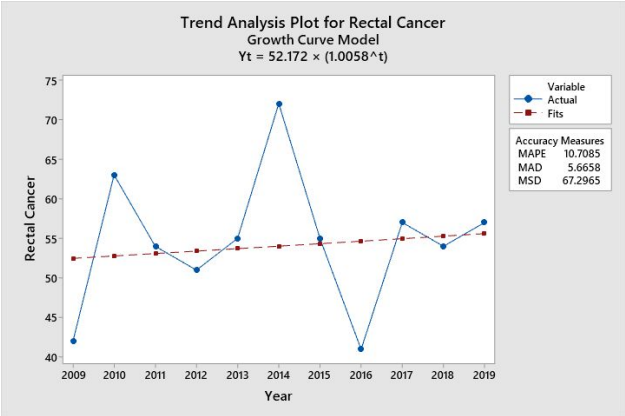
Period	Forecast
2020	51.206
2021	56.018
2022	61.297
2023	67.041
2024	73.252
2025	79.929
2026	87.072
2027	94.681
2028	102.757
2029	111.298
Mean	78.4551
Total	784.551

c. Regression Model for Rectal Cancer Cases Among Old Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear*	**Yt = 53.11 + 0.255t**	**10.5491**	**5.5074**	66.8562
Quadratic	$Yt = 47.5 + 2.86t - 0.217t^2$	10.9428	5.7462	**63.1906**
Exponential Growth	$Yt = 52.172 \times (1.0958^t)$	10.7085	5.6658	67.2965
S-shaped	Error: Can not fit model to these data	n/a	n/a	n/a

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Linear curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.127	1	7.127	.087	.774
Residual	735.418	9	81.713		
Total	742.545	10			

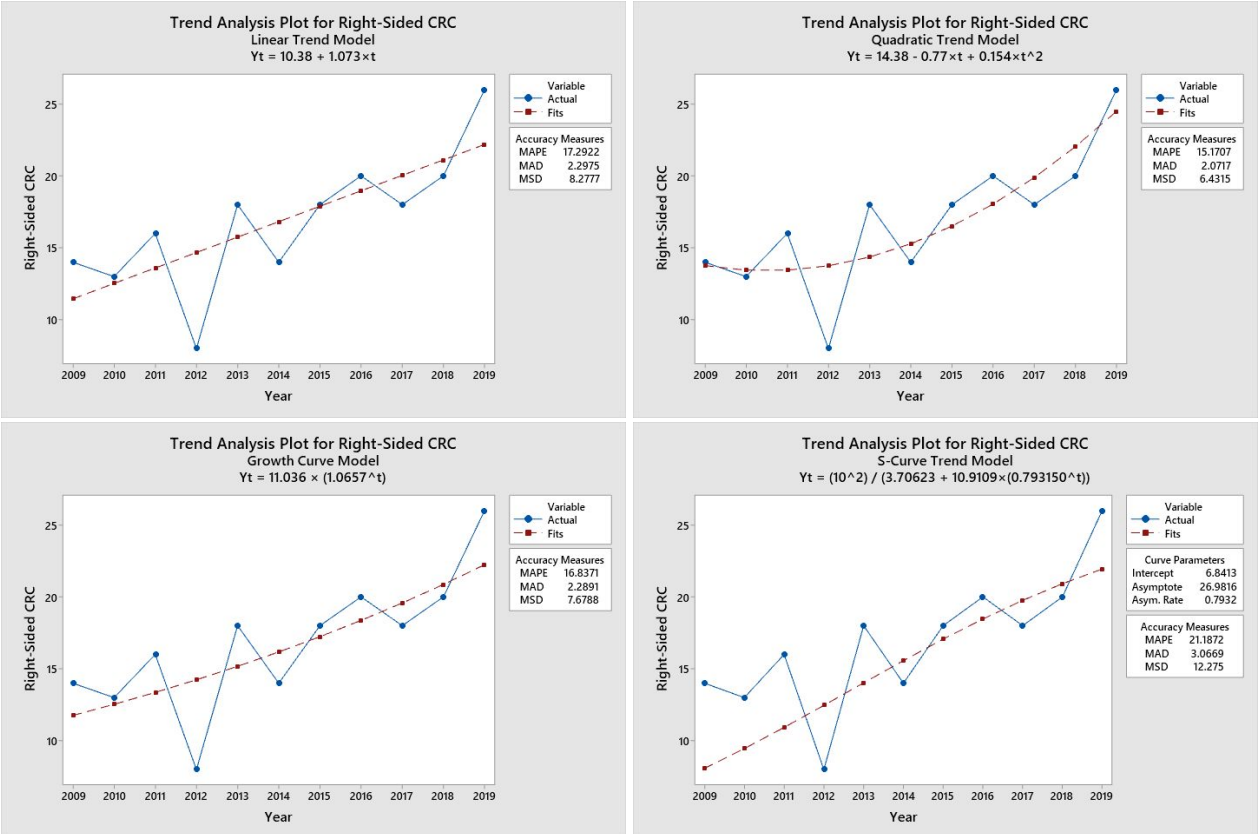
The independent variable is Year.

3. Forecasting following ten-year cases using Linear curve model.

Period	Forecast
2020	56.1636
2021	56.4182
2022	56.6727
2023	56.9273
2024	57.1818
2025	57.4364
2026	57.6909
2027	57.9455
2028	58.2000
2029	58.4545
Mean	57.30909
Total	573.0909

d. Regression Model for Right-Sided CRC Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 10.38 + 1.073t	17.2922	2.2975	8.2777
Quadratic*	**$Yt = 14.38 - 0.77t + 0.154t^2$**	**15.1707**	**2.0717**	**6.4315**
Exponential Growth	$Yt = 11.036 \times (1.0657^t)$	16.8371	2.2891	7.6788
S-shaped	$Yt = 10^2 / (3.70623 + (10.9109 \times 0.793150^t))$	21.1872	3.0669	12.2758

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (Quadratic curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	126.652	1	126.652	12.528	**.006**
Residual	90.984	9	10.109		
Total	217.636	10			

The independent variable is Year.

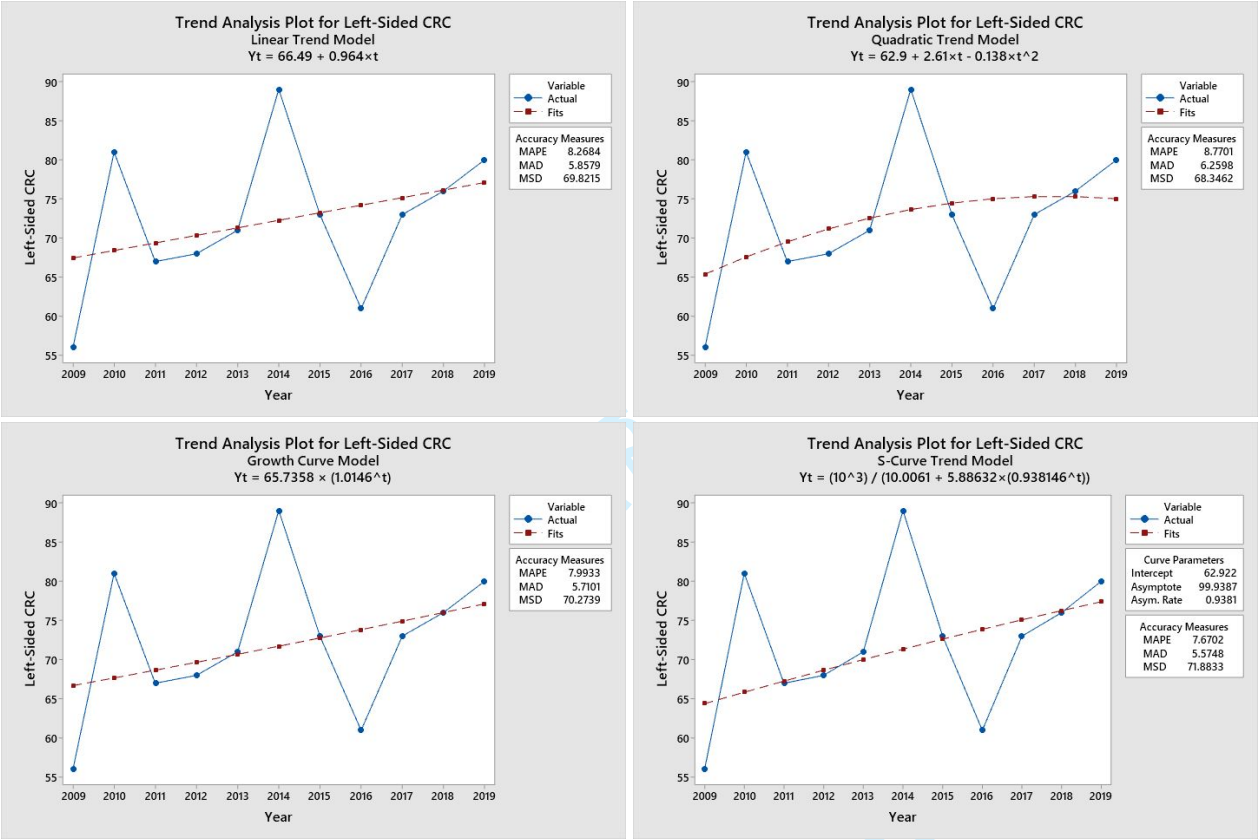
3. Forecasting following ten-year cases using Quadratic curve model.

Period	Forecast
2020	27.2545
2021	30.3273
2022	33.7077
2023	37.3958
2024	41.3916

2025	45.6951
2026	50.3063
2027	55.2252
2028	60.4517
2029	65.9860
Mean	44.77412
Total	447.7412

e. Regression Model for Left-Sided CRC Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 66.49 + 0964t	8.2684	5.8579	69.8215
Quadratic	$Yt = 62.8 + 2.61t - 0.138t^2$	8.7701	6.2598	**68.3462**
Exponential Growth	$Yt = 65.7358 \times (1.0146^t)$	7.9933	5.7101	70.2739
S-shaped*	**$Yt = 10^3 / (10.0061 + (5.88632 \times 0.938146^t))$**	**7.6702**	**5.5748**	71.8833

**the best fitted model is the one who has the lower values for three parameters (MAPE, MAD, and MSD), or at least for two parameters, or having the lowest value for MAPE*

2. Significance test for slope of curve estimation (S-shaped curve model) using ANOVA test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.023	1	.023	1.400	.267

Residual	.149	9	.017		
Total	.172	10			

The independent variable is Year.

3. Forecasting following ten-year cases using S-shaped curve model.

Period	Forecast
2020	78.4808
2021	79.5371
2022	80.5543
2023	81.5325
2024	82.4720
2025	83.3733
2026	84.2369
2027	85.0636
2028	85.8540
2029	86.6090
Mean	82.77135
Total	827.7135

Supplementary Table 1.

Summary of a best-fitted model, predicted case equation, and number of forecasting cases during the period between 2020 and 2029.

	Young Patients (<50 years old)					Old Patients (≥50 years old)					All Patients				
	Tumor Locations			Side Involvement		Tumor Locations			Side Involvement		Tumor Locations			Side Involvement	
	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC
Best-Fitted Model	Exponential Growth	Exponential Growth	Exponential Growth	Quadratic	Quadratic	Quadratic	Quadratic	Linear	Quadratic	S-shaped	Exponential Growth	Exponential Growth	Exponential Growth	Quadratic	Exponential Growth
Predicted Case Equation	$Yt = 48.2453 \times (1.0198^t)$	$Yt = 9.351 \times (1.0924^t)$	$Yt = 39.85 \times (0.9903^t)$	$Yt = 2.79 + 1.86t - 0.113t^2$	$Yt = 46.33 - 1.26t + 0.161t^2$	$Yt = 77.3 + 1.84t + 0.016t^2$	$Yt = 29.82 - 1.02t + 0.233t^2$	$Yt = 53.11 + 0.255t$	$Yt = 14.38 - 0.77t + 0.154t^2$	$Yt = 10^3 / (10.0061 + (5.88632 \times 0.938146^t))$	$Yt = 126.023 \times (1.0223^t)$	$Yt = 34.58 \times (1.0638^t)$	$Yt = 92.3161 \times (0.9991^t)$	$Yt = 17.17 + 1.08t + 0.041t^2$	$Yt = 108.176 \times (1.0141^t)$
MAPE	10.9230	20.8294	9.3215	34.2056	11.9922	7.4248	7.2590	10.5491	15.1707	7.6702	8.8462	9.1430	9.042	17.8277	8.952
MAD	6.2589	3.7308	3.5723	2.8790	5.4062	6.4832	2.40093	5.5074	2.0717	5.5748	12.1	4.9466	8.529	4.2554	10.694
MSD	61.3589	19.9062	23.4688	11.7923	38.5144	67.3214	8.26099	66.8562	6.4315	71.8833	218	41.4342	140.117	26.4743	169.916
p-value of slope	0.200	0.005	0.477	0.217	0.342	0.043	0.001	0.774	0.006	0.267	0.062	<0.001	0.948	0.018	0.252
2020	61.08	27.00	35.47	8.79	54.40	101.73	51.21	56.16	27.25	78.48	162.81	72.65	91.35	36.04	127.94
2021	62.29	29.50	35.13	7.82	57.16	103.98	56.02	56.42	30.33	79.54	166.27	77.29	91.27	38.15	129.74
2022	63.53	32.23	34.79	6.62	60.25	106.26	61.30	56.67	33.71	80.55	169.79	82.22	91.19	40.33	131.56
2023	64.79	35.20	34.45	5.20	63.66	108.58	67.04	56.93	37.40	81.53	173.37	87.47	91.11	42.60	133.42
2024	66.07	38.46	34.12	3.55	67.38	110.92	73.25	57.18	41.39	82.47	177.00	93.05	91.03	44.94	135.29
2025	67.38	42.01	33.79	1.68	71.44	113.30	79.93	57.44	45.70	83.37	180.68	98.99	90.95	47.37	137.20
2026	68.72	45.89	33.46	-0.42	75.81	115.71	87.07	57.69	50.31	84.24	184.43	105.31	90.87	49.88	139.13
2027	70.09	50.13	33.14	-2.75	80.50	118.16	94.68	57.95	55.23	85.06	188.25	112.03	90.79	52.48	141.09
2028	71.48	54.76	32.82	-5.30	85.52	120.64	102.76	58.20	60.45	85.85	192.12	119.18	90.71	55.15	143.08
2029	72.90	59.82	32.50	-8.08	90.85	123.15	111.30	58.45	65.99	86.61	196.05	126.78	90.63	57.91	145.09
Total ten years	66.83	41.50	33.97	1.71	70.70	112.24	78.46	57.31	44.77	82.77	191.07	97.50	90.99	46.49	136.35
Mean per year	668.32	415.01	339.68	17.11	706.97	1122.43	784.55	573.09	447.74	827.71	1910.75	974.96	909.89	464.85	1363.53

Notes:

- Y_t is the variable (equation for predicted cases) and t is the value of the time unit (year).
- The best-fitted model and predicted case equation was decided from the one who has the lower accuracy for three parameters (MAPE, MAD, and MSD) measurement or at least two parameters was the lowest or having the lowest value for MAPE.
- p-value was obtained from the ANOVA test for curve estimation

Abbreviation:

CRC, colorectal cancer; MAPE, mean absolute percent error; MAD, mean absolute deviation; MSD, mean square deviation.

Research Checklist
STROBE Checklist 2007 (v4) Statement For Reporting A Cross-Sectional Study

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	2-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-3
Bias	9	Describe any efforts to address potential sources of bias	16
Study size	10	Explain how the study size was arrived at	2-3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4
		(b) Give reasons for non-participation at each stage	4-5
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-8
		(b) Indicate number of participants with missing data for each variable of interest	4
Outcome data	15*	Report numbers of outcome events or summary measures	4-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4-8
		(*b*) Report category boundaries when continuous variables were categorized	4-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a	N/A

		meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	1-2, and 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

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Analyzing Eleven Years of Incidence Trends, Clinicopathological Characteristics, and Forecasts of Colorectal Cancer in Young and Old Patients: A Retrospective Cross-Sectional Study in An Indonesian National Referral Hospital.

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Analyzing Eleven Years of Incidence Trends, Clinicopathological Characteristics, and Forecasts of Colorectal Cancer in Young and Old Patients: A Retrospective Cross-Sectional Study in An Indonesian National Referral Hospital.

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Running Title: Trends of Colorectal Cancer in Indonesian Patients

Abstract

Objective: To obtain annual incidence trends, understand clinicopathological characteristics, and forecast the future burden of colorectal cancer (CRC) in Indonesia.
Design: 11-year retrospective cross-sectional study.
Setting: A national referral hospital in Jakarta, Indonesia.
Participants: Data from 1,584 eligible cases were recorded for trends and forecasting analyses; 433 samples were analyzed to determine clinicopathological differences between young (<50 years) and old (≥50 years) patients.
Methods: Trend analyses were done using Joinpoint, expressed in annual percentage change (APC), and a regression analysis was executed to generate a forecasting model. Patients' characteristics were compared using chi-square or nonparametric tests.
Main outcomes: Analysis of trends, forecasting model, and clinicopathological features between the age groups.
Results: A significant increase in APC was observed among old patients (+2.38%) for CRC cases. Colon cancer increased remarkably (+9.24%) among young patients; rectal cancer trends were either stable or declining. The trend for right-sided CRC increased in the general population (+6.52%) and old patients (+6.57%), while the trend for left-sided CRC was stable. These cases are expected to be a significant health burden within the next ten years. Patients had a mean age of 53.17±13.94, 38.1% were young, and the sex ratio was 1.21. Prominent characteristics were left-sided CRC, tumor size ≥5 cm, exophytic growth, adenocarcinoma, histologically low-grade, pT3, pN0, inadequately dissected lymph nodes (LN), LN ratio (LNR) <0.05, no distant metastasis, early-stage cancer, no lymphovascular invasion (LVI), and no perineural invasion (PNI). Distinct features between young and old patients were found in the subtype, histology, number of dissected LN, and PNI of the tumor.
Conclusions: Epidemiological trends and forecasting analyses of CRC cases in Indonesian patients showed an enormous increase in colon cancer in young patients, a particularly concerning trend. Additionally, young patients exhibited particular clinicopathological characteristics that contributed to disease severity.
Keywords: clinicopathological characteristics, colorectal cancer, histopathological characteristics, Indonesia, retrospective analysis, young patients, trend analysis.

Strengths and limitations of this study

- This is the first retrospective cross-sectional study of Indonesian colorectal cancer (CRC) patients with a substantial data coverage period from 2009 to 2019.

- We provide trend analysis to determine changes in the annual incidence of CRC in Indonesia based on age, tumor location, and side involvement of cancer, along with a CRC forecasting model to estimate case patterns over the next ten years.
- This epidemiological study comprehensively analyzed the difference in clinicopathological characteristics of CRC in young and old patients.
- Data were taken from a single center and might not be fully representative of other centers in Indonesia. Also, being a retrospective study, this study is susceptible to record bias and data loss from medical record retention and deterioration of microscope slides.
- Data that could help explain the CRC trends, such as lifestyle, diet, alcohol use, tobacco use, family history, hereditary cancer syndromes, socioeconomic characteristics, and diagnostic test frequency, were not recorded.

Introduction

Colorectal cancer (CRC) is the fourth most common cancer globally and is becoming more common in developing countries.[1] CRC is usually diagnosed through endoscopic biopsy or polypectomy. Microscopic examination is conducted to search for invasions. In the new era of personalized medicine, the role of anatomical pathologists has been dramatically expanded. Their role is no longer limited to providing histopathologic diagnosis but also assessing staging, margins, and prognostic parameters that can only be made available by microscopic examinations such as tumor grade, lymphovascular invasion (LVI), and perineural invasion (PNI). Further research about the pathological characteristics of CRC is essential for treatment approaches and policymaking.

Recent long-term studies discovered that young people under 50 years old are more likely to get colon cancer, especially in high-income countries.[2,3] These studies showed changes in CRC epidemiology clinically, histopathologically, and prognostically.[4] By 2030, the incidence of colon and rectal cancer in young people, for whom routine screening is currently not recommended, is projected to increase by 28-30% and 46-124%, respectively.[5] This phenomenon is presumably due to rapid changes in lifestyle, diet, and genetic alterations in high-risk populations. A study in the US found that cancer incidence rose by 17% in young patients. Similar trends were seen in several Asian countries, including China, Japan, India, and South Korea, where a huge rise in the number of young patients with CRC has been documented.[2,6]

Epidemiological studies on CRC from other parts of Asia, including Southeast Asia, are needed since CRC cases are relatively less researched and are becoming a public health threat. Furthermore, in the population younger than 50, CRC shows a rising incidence and appears to display a more aggressive phenotype with unique genetic profiles, critical differences in somatic gene mutations, and gene methylation.[7] Distinct molecular carcinogeneses and genomic profiles of CRC in Indonesia drove us to present a broader view of CRC in terms of epidemiology and clinicopathological characteristics,[8–10] which has not been published by any previous thorough investigation in Indonesia. These knowledge gaps motivated us to research how colorectal cancers have changed from 2009 to 2019 in young patients compared to their older counterparts. We also aimed to obtain annual incidence trends, understand clinicopathological characteristics, and forecast the future burden of CRC in Indonesia.

Materials and Methods

Study Design, Ethical Clearance, Data Collection, and Selection Process

This retrospective cross-sectional study was conducted at the Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, to analyze CRC incidence from 2009 to 2019 using pathological archives and hospital medical records. Ethical approval (KET-139/UN2.F1/ETIK/PPM.00.02/2020, protocol number: 10-11-1416) was obtained from the Institutional Ethical Review Board (IERB) of the Faculty of Medicine, Universitas Indonesia. General consent for the use of medical record data and residual material had already

been obtained, in line with ethical approval.[11–13] Data from 2020 were not included to avoid bias due to the COVID-19 pandemic, which caused a decrease in the number of CRC patients attending the hospital. In total, 1,958 patients have had a malignant tumor of the colon or rectum based on ICD-10 topography (C18-C20) and morphology (M8140/3, M8480/3, and M8490/3) codes with adequate biopsy or resection specimens eligible for enrollment in this study.[14] For the analysis of trends, forecasting, and clinical data, 1,584 patients were selected by exclusion criteria (i.e., duplication of inputted cases, change of diagnosis, or metastasis), with 433 resection samples undergoing a further analysis of pathological characteristics between two age groups, as shown in **Figure 1.**

<**Figure 1.**>

Extraction and Definition of Variables

The variables of age, registration year, sex, tumor location, site, side involvement, and specimen type were extracted directly from cancer registry data. Data on tumor size, growth pattern, histological subtypes, and metastasis characteristics were retrieved from hospital medical records and pathological reports of patients who underwent surgery.

The young patient population was defined as subjects under 50 years of age, agreeing with previous studies.[15] Pathological specimens of each patient were examined under the microscope by two independent pathologists who recorded the histopathology characteristics of pathological tumor staging, histological subtypes, growth pattern, tumor grade, LVI, and PNI. We evaluated the number of dissected lymph nodes (LNs) in agreement with other studies and WHO guidelines, with a minimum of 12 LNs taken for each case.[16–18] Along with LNs, we also calculated the lymph node ratio (LNR), defined as the number of positive LNs divided by the number of LNs examined. LNR was a significant predictor of survival in other malignancies and could be classified into subgroups according to the following cutoffs: <0.05 (LNR1), 0.05–0.20 (LNR2), 0.20–0.40 (LNR3), and 0.40–1.00 (LNR4).[19]

The tumor site was defined as the location where the primary tumor originated. A category of cancers known as right-sided CRC (RSCRC) originated from the caecum, ascending colon, hepatic flexure, and transverse colon. Meanwhile, left-sided CRC (LSCRC) originated from the splenic flexure, descending colon, sigmoid colon, and rectum.[20] Cancer of the caecum, ascending colon, or transverse colon was referred to as proximal colon cancer. The descending colon or the sigmoid colon were the sites of distal colon cancer.[14,21] Tumor size was defined as the largest dimension of the three-dimensional tumor, classified into <5 cm and ≥5 cm. Metastasis (distant metastasis) was confirmed by radiography or pathological diagnostic procedure. The World Health Organization (WHO) guideline and the American Joint Committee on Cancer (AJCC) 8th edition were the basis for pathological staging.[17,18] Tumors with a stage of pT3-T4 or a pathological staging of pTNM III-IV were considered to be in the advanced stage.[17,18] Tumors were also divided into three categories based on their subtypes: adenocarcinoma not otherwise specified (NOS), mucinous adenocarcinoma, and signet-ring cell carcinoma. The tumor growth pattern was classified into exophytic, endophytic, ulcerative, and linitis plastica.[22] According to a WHO categorization based on the percentage of gland formation in the tumor mass, tumor grade was grouped as well-differentiated, moderately differentiated, and poorly differentiated.[17] LVI and PNI were defined as the occurrence of each parameter in at least one slide of the pathology specimen sample.[23]

Statistical Analysis and Presentation of Data

To address the missing data, we performed a sub-analysis for each outcome measured during the sampling process (Figure 1). A comprehensive dataset from biopsy and resection specimens was utilized to extrapolate the CRC trend over eleven years and conduct a comparative analysis of the recorded variables. In order to conduct a more thorough analysis of pathological data, we used only resection specimens. Missing data from the retention of the medical records and deteriorated slides were omitted.

Data were then recorded and processed using the Statistical Package for Social Sciences (SPSS) v.25.0 statistical software with Chi-Square and its alternative tests (Fisher's exact, Kruskal-Wallis, or Mann-Whitney tests). Analysis was performed for the young and old patient populations for clinicopathological characteristics. The mean value of quantitative parameters (number of positive and dissected LNs, LNR, and tumor size) was compared between two age groups with the t-student test. Annual incidence rates were quantified using the Joinpoint regression package provided by the US National Cancer Institute Surveillance Research Program and National Cancer Institute (version 4.9.1.0).[24] Joinpoint regression analysis, established by Kim and colleagues[25], is a well-known approach used to study varying trends over time with Bonferroni adjustment.[26] It automatically joined separated time series of points (years) of cases on a logarithmic scale, expressed the trends as an annual percentage change (APC), and therefore quantified the short-term increase or decrease between two successive points of change.[24,25] A Monte Carlo permutation test assessed the significance of changing trends (i.e., APC).[27] Joinpoint regression analysis might be employed when the temporal trend of a given quantity (e.g., proportions, rates, counts), such as incidence and mortality (e.g., referring to cancer-related scenarios), was of interest.[28–30] It is valuable to generate quantitative inferences instead of qualitative ones in epidemiological studies.[24,31]

We also performed linear and non-linear regression analyses to construct the best-fitted model to forecast the increasing trend of CRC cases in the next ten years (2020–2029) using Minitab® 19.1 (64-bit).[32–38] The model trend equation to predict CRC cases can be visualized in linear [$Y_t = b_0 + (b_1 * t)$], quadratic [$Y_t = b_0 + b_1 * t + (b_2 * t^2)$], exponential [$Y_t = b_0 + (b_1^t)$], or S-curve (Pearl-Reed logistic) [$Y_t = (10^a) / (b_0 + b_1 * b_2 t)$] functions, with Y_t being the variable, b_0 being a constant, b_1 and b_2 being coefficients, and t as the value of the time unit. The best-fitted model is the model which has the lower values for three of these parameters: MAPE, mean absolute percent error; MAD, mean absolute deviation; and MSD, mean square deviation, or at least for two parameters, or having the lowest value for MAPE.[36,39,40] The MAPE expresses accuracy as a percentage of the error. The MAD expresses accuracy in the same units as the data, which helps conceptualize the amount of error. The MSD measures the accuracy of the fitted time series. After deciding on the models, we measured the significance of their slope using the ANOVA test for curve estimation in SPSS. Statistical analyses with a p-value <0.05 and a 95% confidence interval (CI) for probability were considered significant.

Patient and Public Involvement Statement

It was not possible to involve patients or the public in our research's design, conduction, reporting, or dissemination plans. This report complied with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies (including cross-sectional studies), as stated in the **Research Checklist**.[41]

Results

Of the 1,584 people diagnosed with CRC in this study, males dominated the CRC cases registered in our center, with a sex ratio (male: female) of 1.21. Distribution based on age groups, as shown in **Table 1,** demonstrated that the highest proportion of CRC was found in ages 51–60 years old; the mean age was

53.17 ± 13.94 years old, with females (52.28 ± 13.98 years old) generally being younger than males (53.90 ± 13.89 years old), p=0.021. Looking at the more specific age groupings, we found that the number and proportion of our patients' age was: 11–20 (11; 0.7%), 21–30 (81; 5.8%), 31–40 (225; 14.2%), 41–50 (339; 21.4%), 51–60 (432; 27.3%), 61–70 (334; 21.2%), 71–80 (135; 8.5%), 81–90 (20; 1.3%), and ≥91 (7; 0.4%). The mean age of the young patient population was surprisingly very young (38.82 ± 7.46 years old). The proportion of young patients in this center reached 38.10% (n = 604) of the total incidence (n = 1,584). The biggest proportion of CRC in our center was rectal cancer (64.3% vs. 35.7%). Proximal and distal colon cancer were similar in number (49.6% vs. 50.4%). LSCRC was still higher in proportion (82.3%). The sigmoid colon is the most often affected area.

Table 1. Clinicopathological characteristics of tumors in young and old patients (n = 1,584)

Characteristics	Young patients (<50 y.o.) (n=604)		Old patients (≥50 y.o.) (n=980)		All patients (n=1,584)		p-value
	N	%	n	%	N	%	
Registration year							0.931[a]
2009	49	8.1	70	7.1	119	7.5	
2010	52	8.6	94	9.6	146	9.2	
2011	47	7.8	83	8.5	130	8.2	
2012	52	8.6	76	7.8	128	8.1	
2013	50	8.3	89	9.1	139	8.8	
2014	69	11.4	103	10.5	172	10.9	
2015	64	10.6	91	9.3	155	9.8	
2016	48	7.9	81	8.3	129	8.1	
2017	47	7.8	91	9.3	138	8.7	
2018	54	8.9	96	9.8	150	9.5	
2019	72	11.9	106	10.8	178	11.2	
Sex							0.056[a]
Male	313	51.8	556	56.7	869	54.9	
Female	291	48.2	424	43.3	715	45.1	
Tumor site							**0.002[a]**
Colon	187	31.0	379	38.7	566	35.7	
Rectal	417	69.0	601	61.3	1,018	64.3	
Tumor location							0.572[a]
Proximal colon	96	51.3	185	48.8	281	49.6	
Distal colon	91	48.7	194	51.2	285	50.4	
Side involvement							0.131[a]
RSCRC	96	15.9	185	18.9	281	17.7	
LSCRC	508	84.1	795	81.1	1,303	82.3	
Tumor subsites							**0.002[a]**
Caecum	20	3.3	58	5.9	78	4.9	
Ascending colon	52	8.6	75	7.7	127	8.0	
Transverse colon	24	4.0	52	5.3	76	4.8	
Descending colon	33	5.5	46	4.7	79	5.0	
Sigmoid	58	9.6	148	15.1	206	13.0	
Rectum	417	69.0	601	61.3	1,018	64.3	
Specimen							0.135[a]
Biopsy	267	44.2	471	48.1	748	46.6	
Resection	337	55.8	509	51.9	846	53.4	

[a]Independent samples t-test [a]Chi-Square test; *Significant value for all tumor subsites

Figure 2 elucidates changes in the trend of CRC cases in Indonesian patients (denoted as an APC) over eleven years among all patients, as well as subcategorized by age groups (i.e., young and old patients), anatomical location of the tumor (i.e., colon, rectum, or colon plus rectum) and side involvement of CRC (right-sided vs. left-sided). Using Joinpoint regression analysis, a significant APC was observed among all patients, specifically in the annual incidence of colon cancer (+6.38%) and RSCRC (+6.52%). Among young patients, notable APC was only found in colon cancer (+9.24%); meanwhile, in the old patient group, a remarkable APC was noticed in CRC as a whole (+2.38%), colon cancer (+5.11%), and RSCRC (+6.57%). Trend patterns were positive for all CRC sites, except the rectum, which experienced stagnation in old patients (+0.58%) and dropped among the general population (–0.09%) and young patients (–0.97%) with $p>0.05$. More detailed data on the trend analysis of our CRC patients have been provided in **Supplementary Files 1-3**.

<**Figure 2.**>

This study also investigated the increase of colon cancer based on their subsites (i.e., caecum, ascending colon, transverse colon, descending colon, and sigmoid colon), which is visualized in **Figure 3**. Significantly positive APC values were observed highest in the ascending colon (+10.60%), followed by the descending colon (+10.04%), the transverse colon (+9.88%), and the sigmoid colon (+5.84%).

<**Figure 3.**>

Additionally, as illustrated in **Figure 4,** several forecasting models of CRC incidences were generated using the best-fitted regression analysis**.** This approach predicted subsequent ten-year annual incidence rates for CRC cases using a specific case-equation-formula. The linearity of cancer incidence trends over eleven years based on our institutional cancer registry data was evaluated with the p-value for the slope in linear regression models. P-values from ANOVA tests for curve estimation of the slope were reported for each regression. The precise number of predicted cases for the next ten years (2020–2029) can be found in **Supplementary Files 4-6** and **Supplementary Table 1**. The average future burden of CRC from 2020 to 2029 compared to the current 11-year data in all, young, and old patients (**Table 2)** was ~180 cases/year (vs. 144 cases/year), ~67 cases/year (vs. 55 cases/year), and ~112 cases/year (vs. 89 cases/year) respectively.

<**Figure 4.**>

As described in **Table 2**, most tumor sizes were equal to or more than 5 cm (61%), with a predominant brown color. Distant metastasis occurred in 6.9% of all cases. Most tumors were exophytic lesions (83.1%), adenocarcinoma NOS (85.2%), well-differentiated (67.7%), with a pathological tumor staging of pT3 (66.5%), having inadequately dissected LN (56.4%) and LNR1 (57.5%), tumor stage IIA (34.2%), early stage (55.2%), without LVI (61.7%) and PNI (88.7%). Comparing young and old patients, we found no significant differences in clinicopathological and histopathological characteristics except for histological subtypes, adequacy of LN sampling, and PNI. Adenocarcinoma NOS is most prevalent in old patients, while the mucinous variant dominates in young patients ($p<0.05$). Old patients were more likely to have inadequately dissected LN than young patients ($p<0.01$). Young patients had more PNI than their older counterparts ($p<0.001$).

Table 2. Pathological characteristics of tumor in young and old patients who underwent surgical resection with complete data (n=433)

Characteristics	Young patients (<50 y.o.) (n=144)		Old patients (≥50 y.o.) (n=289)		All patients (n=403)		p-value
	n	%	n	%	n	%	
Tumor size							0.559[a]
<5 cm	59	41.0	110	38.1	169	39.0	
≥ 5 cm	85	59.0	179	61.9	264	61.0	
Growth pattern							0.814[b]
Exophytic	120	83.3	240	83	360	83.1	
Endophytic	15	10.4	21	7.3	36	8.3	
Ulcerative	8	5.6	22	7.6	30	6.9	
Linitis Plastica	1	0.7	6	2.1	7	1.6	
Histological subtypes							**0.025[b]**
Adenocarcinoma NOS	115	79.9	254	87.9	369	85.2	
Mucinous	19.4	19.4	35	12.1	63	14.5	
Signet-Ring Cell	0.7	0.7	0	0.0	1	0.2	
Tumor grade							0.591[a]
Well-differentiated	97	67.4	196	67.8	293	67.7	
Moderately differentiated	31	21.5	69	23.9	100	23.1	
Poorly differentiated	16	11.1	24	8.3	40	9.2	
Pathological tumor staging							0.587[b]
pT1	3	2.1	8	2.8	11	2.5	
pT2	22	15.3	44	15.2	66	15.2	
pT3	94	65.3	194	67.1	288	66.5	
pT4	25	17.4	14.9	14.9	68	15.7	
Pathological node status							0.734[a]
pN0	80	55.6	168	58.1	248	57.3	
pN1a	18	12.5	42	14.5	60	13.9	
pN1b	18	12.5	34	11.8	52	12.0	
pN2a	18	12.5	33	11.4	51	11.8	
pN2b	10	10.0	12	4.2	22	5.1	
Adequacy of dissected node							
Inadequate (<12)	67	46.5	177	61.2	244	56.4	**0.004[a]**
Adequate (≥12)	77	53.5	112	38.8	189	43.6	
Lymph node ratio (LNR)							0.967[a]
LNR1 (<0.05)	81	56.3	168	58.1	249	57.5	
LNR2 (0.05-0.20)	21	14.6	38	13.1	59	13.6	
LNR3 (0.20-0.40)	15	10.4	28	9.7	43	9.9	
LNR4 (≥0.40)	27	18.8	55	19.0	82	18.9	
Lymph Node Metastasis							0.610[a]
Yes	80	55.6	168	58.1	248	57.3	
No	64	44.4	121	41.9	185	42.7	
Distant Metastasis							0.110[a]
M0	138	95.8	265	91.7	403	93.1	
M1	6	4.2	24	8.3	30	6.9	
Staging							0.431[a]
I	19	13.2	41	14.2	60	13.9	
IIA	48	33.3	100	34.6	148	34.2	
IIB	12	8.3	19	6.6	31	7.2	
IIIA	6	4.2	10	3.5	16	3.7	
IIIB	39	27.1	83	28.7	122	28.2	
IIIC	15	10.4	16	5.5	31	7.2	
IV	5	3.5	20	6.9	25	5.8	
Degree of Staging							0.921[a]
Early stage (I-II)	79	54.9	160	55.4	239	55.2	
Advanced stage (III-IV)	65	45.1	129	44.6	194	44.8	

Lymphovascular invasion							0.314[a]
Negative	84	58.3	183	63.3	267	61.7	
Positive	60	41.7	106	36.7	166	38.3	
Perineural invasion							**<0.001[a]**
Negative	114	79.2	270	93.4	384	88.7	
Positive	30	20.8	19	6.6	49	11.3	

[a] Chi-Square; [a] Mann-Whitney; Percentage of the total column; NOS, nonspecific

We detected a significant difference in mean age (more than 23 years) between the young and old patient groups, as described in **Table 3**. Additionally, the number of dissected LNs was significantly higher in the young patient group compared to the old patient group.

Table 3. Comparison of the mean value of clinicopathological parameters of tumor between young and old patients

Parameters	Mean ± SD or Number			p-value
	Young patients (<50 y.o.)	Old patients (≥50 y.o.)	All patients	
CRC cases per year	54.91 ± 9.07	89.09 ± 10.94	144.00 ± 18.61	
Colon cancer cases per year	17.00 ± 6.93	34.45 ± 6.98	51.45 ± 13.05	
Rectal cancer cases per year	37.91 ± 5.20	54.64 ± 8.62	92.55 ± 12.40	
RSCRC cases per year	8.73 ± 4.10	16.82 ± 4.67	25.55 ± 7.15	
LSCRC cases per year	46.18 ± 7.04	72.27 ± 9.33	118.45 ± 14.69	
Age (years old)*	38.82 ± 7.46	62.01 ± 8.65	53.17 ± 13.94	**<0.001[a]**
Tumor size (cm)[#]	5.92 ± 3.12	5.99 ± 2.98	5.97 ± 3.02	0.818[a]
Smallest tumor size (cm)[#]	1.3	1.0	1.0	
Largest tumor size (cm)[#]	17.0	18.0	18	
Total count of positive LNs[#]	265	402	667	
Total count of dissected LNs[#]	1,587	2,726	4,313	
Positive LNs[#]	1.84 ± 3.37	1.39 ± 2.34	1.54 ± 2.73	0.107[a]
Dissected LNs[#]	11.02 ± 6.10	9.43 ± 5.04	9.96 ± 5.46	**0.004[a]**
LNR [#]	0.18 ± 0.29	0.18 ± 0.30	0.18 ± 0.29	0.964[a]

[a]Independent samples t-test for equality of means (2-tailed)

*Assessed among 1,584 patients

[#]Assessed among 433 patients

*Abbreviation: CRC, colorectal cancer; LNs, lymph nodes; LNR, lymph node ratio; RSCRC, right-sided colorectal cancer; LSCRC, left-sided colorectal cancer

Figure 5 describes the histopathological features of our CRC cases. Descriptive proportions are presented in **Tables 1, 2,** and **3.**

<**Figure 5.**>

Discussion

This observational study was conducted to assess clinical trends of CRC over 11 years, forecast the future burden of CRC over the next ten years, and analyze the pathology of 1,584 CRC cases in a national referral hospital in Indonesia. The current investigation corroborated previous findings regarding men's predominance in CRC incidence. This could be because men are more likely to smoke and drink alcohol (both of which are risk factors for CRC), whereas women have higher levels of endogenous estrogens, which protect against CRC carcinogenesis.[42] Our study found that most CRC cases were identified in the middle-aged population, with peak incidence occurring between 51–60 years old, consistent with previous findings.[43] Female patients had a mean age younger than male patients, consistent with findings from an

investigation conducted in Brunei Darussalam.[44] The definition of "young patients" in an epidemiological study of CRC is arbitrary; we used 50 years as the cutoff age since this is the recommended age for first CRC screening in most screening programs that have gained global adoption.[15] Early-onset CRC is more likely to arise sporadically in third-world nations and is hypothetically a biologically and clinically unique entity, accounting for its aggressive presentation and poor prognosis.[45–47] We report that CRC incidence among young patients reached nearly 40%, significantly higher than the rate reported in a previous Indonesian study on CRC between 2014 and 2016 with 275 samples (31.3%),[48] Western countries (7%),[49] and other Asian studies (6.7–35.5%).[50,51] Other findings from South Asia were comparable to ours, with CRC incidence in young individuals ranging from 38% to 52%.[46,52] The increasing proportion of young patients in our population may be influenced by the demographic profile of Indonesia, which had a high proportion of people aged 50 or lower in 2019 (213,984,600 of 268,074,600; percentage: 79.82%).[53]

1. Trend Analysis of CRC

The Joinpoint regression has significant analytic advantages for disease surveillance and, therefore, is valuable to portray trends in CRC incidence over time. Furthermore, it is already widely used in CRC trend analyses in many regions of the world, including North America (USA[54] and Canada[55]), Latin America (Brazil[56] and Mexico[57]), Europe (e.g., England[58], Spain[59], and Netherland,[60]), East Asia (e.g., China[61] and South Korea[62]), the Middle East (e.g., Iran[63] and Lebanon[64]), and Southeast Asia (e.g., Vietnam[65] and Thailand[66]). In our investigation, the Joinpoint regression analysis allowed for identifying patterns of short-term trends that differed between young and old patients. CRC incidence rates were modestly elevated in all and young patients with APC +2.23% and +1.98%, respectively. The rise of cases among subjects aged ≥50 years was statistically significant, with an APC of +2.38% (p=0.041). Indonesia experienced a more significant increase in CRC incidence among old patients.[6] A similar conclusion was reached by Pham et al[65] in the Vietnamese population (APC +5.3%; 95% CI 2.8–7.9%). Hypothetically, this might happen because older patients were more likely to be included in screening programs than young patients.[65] Since the population-based CRC screening program has not been implemented in routine clinical practice in Indonesia, the actual rate of early-onset CRC might have been undervalued. The estimated cost of treatment for CRC patients in Indonesia is $116,083.37,[67] representing 0.000011% of the gross domestic product (GDP) in 2020.[68] The cost burden of treatment increases significantly as the disease progresses. In terms of screening costs, colonoscopy and fecal testing range from $207–765 and $2.75–11, respectively. Given the high cost of treatment, rising CRC incidence, and low cost of screening, our research suggests that Indonesia may benefit from implementing a population-based CRC screening program for high-risk populations, particularly those born after 1980, to detect CRC early and reduce the economic burden.

According to WHO, the prediction of CRC incidence in Indonesia from 2020 to 2025 was higher than the APC of trend analyses done in our study (CRC +17.7% vs. +2.23%, colon cancer +18.1% vs. +6.38%, and rectal cancer +17.3% vs. –0.09%).[69] Also, we found a lower APC in our population than a study conducted in Thailand among young patients between 1989 and 2012 (+5.7%)[66] and a study of CRC patients in Tunisia from 1994 to 2009 (+3.9%).[70] Trend analysis in **Figure 2** reveals a sharp rise in colon cancer annually among young patients with a higher APC than in old and overall patients (+9.24% vs. +5.11% and +6.38%, respectively). In the last few decades, the incidence of CRC has been increasing in Asia, particularly in Southeast Asian countries, including Indonesia and Malaysia.[71] If this trend continues, the number of CRC cases may suddenly overwhelm the healthcare system. Thus, better health policies should be constructed by the government.

The rise of CRC in young patients has not yet been fully elucidated. Early life exposure to the deleterious effects of risk factors, such as frequent smoking, alcohol consumption, obesity, a Western diet, reduced physical activity, and early-life antibiotic exposure, has been thought to increase susceptibility to CRC. Smoking is associated with hypermethylation, microsatellite instability, and BRAF mutations in CRC carcinogenesis.[72] Smoking early in life may play a part in the increasing incidence of CRC observed in young Indonesian people, as frequent daily smoking was found in 13.4% and 27.3% of Indonesian teenagers (95%CI: 12.9–13.9%) and youth (95%CI: 26.8–27.8%) respectively.[73] The risk of CRC is also increased by alcohol consumption, which is positively associated with the risk of distal colon cancer and rectum among the Asian population.[74,75] In Indonesia, alcohol consumption rose strikingly from 2000 to 2020, with the current proportion of alcohol consumption in teenagers and youth being 4.0% (95%CI: 3.8–4.3%) and 6.4% (95%CI: 6.1–6.6%) respectively.[73] Obesity has been linked with a higher risk of colon cancer in Asians. According to national survey data in 2019, overweight and obese individuals comprised roughly 4–8,8% of Indonesians aged 13–18 and nearly 21% of those over 18.[73,76] It is not surprising that the obesity epidemic and the rise in colon cancer happen simultaneously. Many behaviors that are thought to cause weight gain, like unhealthy eating habits and sedentary lifestyles, also raise the risk of CRC. Obesity can promote cancer formation through metabolic abnormalities, hyperinsulinemia, systemic inflammation, and alteration of the gut microbiota.[77] An upward trend in CRC in Indonesia is also probably due to the acquisition of the Western diet.[78] This lifestyle trend has been seen in Indonesian teenagers who consume inadequate amounts of protein, fruits, and vegetables, but excessive amounts of sodium and fast food.[79] A recent study found that the de novo introduction of a Western-style high-fat, low-fiber diet induces inflammation and proliferation in the colonic mucosa within two weeks.[80] Increasing obesity is concurrent with reductions in physical activity levels.[81] A study in Japan found an inverse association between physical activity and CRC, and this association was stronger for colon cancer than rectal cancer.[82] This fact agrees with a survey in Indonesia that found 33.5% (95%CI: 33.3–33.8%) of the Indonesian population lacked suitable physical activity according to time and frequency standards.[73] Another related risk factor for CRC among Indonesians is early-life and improper antibiotic use.[83] These early-life exposures and improper antibiotic use could change the gut microbiota and metabolic profile, making a person more likely to have obesity later in life.[84]

Almost two-thirds of patients had rectal cancer, more common in young (69%) than in old (61.3%) patients. The rectum being the most common tumor site followed by the sigmoid colon is consistent with a previous study conducted in Saudi Arabia.[85] Instead of the proximal colon being a predominant site in young patients, the greater proportion of rectal cancer in our young patients implies additional factors behind these changes. Certain lifestyle factors relevant to young patients have contributed to colorectal carcinogeneses, such as processed meat consumption which is more linked to rectal than colon cancer.[86] We found that the rate of increase differed for colon and rectal cancer, 5.11% to 6.38% for colon cancer compared with 0.58% to 0.97% for rectal cancer. In contrast with colon cancer, rectal cancer incidence has generally declined overall and in the young age group and remains stable in the old age group. These results may be because precancerous lesions or suspected tumors can be found and removed during clinical examination of the rectum in screening. This study has not demonstrated the positive trend of rectal cancer as WHO predicted.[69] Consistent with findings from our study, in Canada, after 1985, rectal cancer incidence slightly declined, with an APC of –0.38% in the general population.[87] The trend of CRC subsite distribution progressively shifting to the proximal colon also occurred in various countries, such as the US (1970–2000),[88] Japan (1974–1994)[89] and Norway (1962–2006).[90]

Our findings emphasize that colon cancer incidence rose faster than rectal cancer in young patients (APC +9.24% vs. –0.97%), similar to results among Canadian young patients from 1969 to 2010 (APC +6.2% vs. +1.5%).[91] The APC of colon cancer in our institution was higher than in Tunisia (+6.38% vs. +4.5%).[70] Some well-known risk factors do not exactly give a similar susceptibility towards colon and rectal cancer. The carcinogenic process may be different depending on where it happens.[87] Diet patterns, physical inactivity, and high body mass index have been linked to a higher risk of colon cancer, but not rectal cancer.[74,92] Meanwhile, smoking and alcohol consumption have been linked to a higher risk of rectal cancer.[93,94] Obesity, insulin resistance, and high blood glucose levels are connected with a higher risk of colon cancer because the colon is more insulin-sensitive than the rectum.[95,96] We also hypothesized that women may have benefited from the preventive effect of hormones against distal colon and rectal cancer. Endogenous hormones may have protected some women from developing distal colon cancer and rectal cancer. Increased use of exogenous hormones, such as hormone replacement therapy or oral contraceptives, may also have resulted in further reductions in these cancers. Between 2005 and 2012, 61% of Indonesian women used contraceptive management.[97] This preventive effect has not been observed for proximal (right-sided) colon tumors.[87]

In contrast to earlier findings and the widely held belief that RSCRC was always more common in young patients, we found that RSCRC was more frequent in old patients, supported by evidence from Germany.[98] Our results showed that most young patients had lesions in the left colon, in agreement with a hospital-based study in the Memorial Sloan Kettering Cancer Center, in the US, where their young patients were more likely to have LSCRC.[99] A cohort study has found that LSCRC occurs worrisomely more frequently after 50 years of age, with a frequency of cases more than that of RSCRC.[20]

The trend analyses in **Figure 2**. show that the APC of RSCRC rose statistically significantly among all patients (+6.52%) and old patients (+6.57%) over the study's eleven-year period, with the largest APC seen in young patients (+6.59%). The causes of these patterns are unknown; they might be due to inconsistent plotting of several incidences each year to follow a particular joined line to figure out a trend. The rising trend of RSCRC from 2009 to 2019 could be influenced by a lack of genetic counseling addressing age, specific syndromes, and family history in Indonesia, as RSCRC is usually associated with a genetic predisposition.[100] It is also challenging to detect nonpolypoid tumors (flat or depressed), more common in the right colon. These lesions are more likely to include carcinoma but are more difficult to detect and occur more frequently in high-risk individuals.[101] Higher colonoscopy miss rates may impede screening and identification of precancer and cancer lesions in the right-side colon, contributing to the rising trend of RSCRC.[102–104] RSCRC has a worse prognosis than LSCRC and rectal cancer.[105] A recent study found left-sided tumors to be increasingly observed in young patients, although not statistically significant among all (APC +1.41%), young (APC +1.37%), and old patients (APC +1.46%), similar to a report from Siegel et al.[106] The clinical implications of different proportion of side involvement between young and old patients was to the aggressiveness of the disease. RSCRCs are typically bulky, exophytic, polypoid lesions projecting into the lumen and causing significant anemia. LSCRCs are infiltrating, constricting lesions encircling the lumen, often leading to obstruction.[107] A study implied that LSCRCs are genetically more unstable and phenotypically more aggressive due to distinct molecular biology patterns between RSCRC and LSCRC in DNA euploidy status, KRAS, and p53 mutation rates.[98]

Observing more specifically the trend of colon cancer based on its subsites, what can be seen in **Figure 3** is the significant growth of 4 of 5 colon subsites during the study period. In our study, the APC of ascending colon rose more quickly than APC in China from 2000 to 2004 (+10.60% vs. +2.25%).[94] The transverse and descending colon had opposite results (+9.88% vs. –1.95% and +10.04% vs. –1.02%,

respectively), while the sigmoid colon had a more positive trend (+5.84% vs. +4.19%).[108] Surprisingly, no differences in APC were found in the caecum (–0.98%), which had a slow and steady decline in cases. These trends aligned with the right-sided dominance during eleven years of study. Different parts of the colon may be more or less vulnerable to carcinogens because of biological differences in the intestine.[109] For example, genetic factors may play a significant role in developing RSCRC, but factors like diet, exercise, and hormone use are more likely linked to LSCRC.[109]

The trend analysis in this study enlightens us to narrow down patients in danger. Given the rapid economic transition and urbanization occurring in Indonesia, it is possible to generalize the upward CRC incidence trend in a single center in Jakarta to all of Indonesia,[110,111] similar to what a study in Vietnam suggested.[65] However, as this is a single-center study, the data presented may not be fully representative of other centers. Further research is needed to see if the trend can be reversed, for example, by evaluating current CRC screening standards and lowering the age at which people should begin screening. To reduce the upward trend, more studies are also required to investigate CRC risk factors in Indonesia. Our current study did not record data on risk factors of CRC that might help explain the trend of CRC found in the study. Furthermore, the cross-sectional design of this study did not allow us to establish any causal relationship.

2. Forecasting the CRC Burden

In **Figure 4**, we forecasted the future burden of CRC by performing a fit-model regression analysis to predict colon and rectal cancer incidences along with RSCRC and LSCRC. The model with a significant slope was found in all and old patients with colon cancer and RSCRC. Meanwhile, in young patients, the model with a significant slope was found only for colon cancer. Projection models for CRC, colon cancer, and rectal cancer follow the exponential growth curve pattern in the overall and young patient groups. While, in the old patient group, colon cancer and CRC forecasting models use the quadratic model. In contrast, the projection model for rectal cancer follows the linear model in the old patient group. Compared to RSCRC, which follows the quadratic model, LSCRC was more varied, with the overall group following the exponential growth curve, the young patients' cases following the quadratic model, and the old patients' cases following the S-shaped model (sigmoid) curve.

The best-fitted model for forecasting CRC cases had different clinical implications based on curve shape. Addressing the interpretation of each curve was challenging since little robust research explains forecasting cancer incidence.[112] A linear trend is a forecasting model that develops a linear relationship between time and the response variable (incidence of disease). The linear model observed in rectal cancer among old patients means that cases increase gradually and linearly at a constant rate over time. This model assumption was based on forecast accuracy metrics and was supported by what has been pictured in trend analysis of rectal cancer with stable APC.[113] What should be highlighted in this paper is that although the rectum was the most prevalent tumor site, we identified a negative trend or stable growth for this site in both Joinpoint analysis and fit-model regression analysis for forecasting, similar to what was reported in Japan (APC –1.9%; CI: –2.6% to –1.1%).[89]

Seven of fifteen scenarios were fitted into the quadratic curve model, a forecasting method that developed a non-linear relationship between time series and the response variable. The quadratic trend resembles a polynomial regression model that accurately captures the data trend.[113] All RSCRC scenarios follow a quadratic model, with a positive trend line of forecasting in all and old patients and a negative trend line in young patients. Forecasting of RSCRC remains upward for the trend until 2029 among all old patients. However, contrary to expectations, this study projected RSCRC to gradually decline in incidence

until 2029 in young patients following the quadratic model as a best-fitted model instead of following the continuous increase in incidence over the previous eleven years. This assumption is similar to a study in the US, which found that RSCRC will increase, remain stable, and decrease by 2.3–2.6% annually.[100] The reasons for these conflicting findings remain unclear but might be explained by the complex attributions of risk factors on a different side of tumor involvement. Increased use of colonoscopy and improved techniques and training for conducting colonoscopy in the right colon to screen, detect, and diagnose may contribute to reducing RSCRC lesions among subclinical diseases in the future.[114] Another possible explanation for this result might be that in 2009–2019, a higher proportion of patients having genetic factors resulted in a higher trend of RSCRC. Nevertheless, in the next ten years, we project that the trend will be shifting to increasing rates of distal cancer due to greater exposure to specific risk factors that cause cancers at these subsites, especially the increasing adoption of a Westernized lifestyle in Indonesia which is also currently occurring in other Asian countries.[65,87,109,115,116] However, RSCRC among old patients is increasing significantly. This linear forecast is similar to the current literature, suggesting that RSCRC is associated with several adverse prognostic factors: older age, advanced stage, and mucinous histological subtype.[20,117,118] We suggest that further studies are needed to find the associated factors for each CRC subsite in Indonesia to explain the subsite and side-involvement incidence trend.

Most cases followed the exponential growth curve as the best-fitted model. This curve has a J-shape, which refers to a growth whose rate is proportional to the size of the population over a specific period. Exponential growth curve modeling is a regression-based method for analyzing longitudinal data (i.e., tracking the same sample at different points in time), suited to the projection of trends in one disease entity into a different period. The advantage of growth curve modeling over other methods is that this technique permits the testing of several types of trajectories until the one with the best fit to the data is found, and an output is far more precise than other statistical means.[119,120] Exponential growth is distinguished by its slow start and, at some point, accelerating growth rate. The exponential growth curve has the fastest growth compared with the S-shaped, quadratic, and linear curves. This pattern causes an explosion of cases, relatively more than the S-shaped, which causes a relatively constant growth rate in the population.

One scenario of LSCRC among old patients following the sigmoid-shaped (S-shaped) curve trend model refers to a case whose growth rate decreases with the increasing number of individuals. It is a forecasting method that develops a sigmoid relationship between time and the response variable.[113] An S-shaped curve is symmetric around the inflection point, which means that the case increases rapidly initially, followed by a slower rate after the inflection point than the rate postulated by the curve. The cases following this pattern will have initial slow growth, a growth explosion, then at their upper limit, cases will be gradually steady. However, this can lead to underestimation and overestimation of the actual disease risk at the lower and upper tails.[121] The S-curve trend model is best for time series that follow a logistic.[113]

Projected CRC cases in Indonesia for the next ten years confirm the future global burden of CRC, which is expected to increase by 60%, to over 2.2 million new cases in 2030.[122] Looking specifically at **Supplementary Table 1** regarding cases predicted for 2020–2029, the burden of CRC remained high in our institution.

3. Distinct Clinical and Pathological Features in Young Patients

Young individuals may be more susceptible to CRC due to genetic alterations and dietary changes; hence molecular profiles of young Indonesian CRC patients have been identified to understand better the specific pathway involved in this group.[8] Our young cases, mainly found in distal locations for CRC, are

not in line with the characteristics of hereditary CRC, primarily found in proximal sites. They also did not follow the conventional pathways of sporadic CRC (the CIN pathway). Instead, carcinogenesis in these patients seems to have originated with MSI and inflammatory pathways, including cyclooxygenase-2 (COX-2) and nucleus factor κB (NF-κB). Also, lower mutation rates of the pro-oncogene KRAS are found among young Indonesian patients.[8] Sudoyo et al[123] found that 56.5% of CRC cases were positively stained for MSH2 and 16.5% stained for MLH1. Moreover, signet-ring cell carcinoma—an aggressive subtype of CRC that spreads rapidly and is characterized by late symptom manifestations—disproportionately affects young individuals.[124] It is also possible that the differences in the immune systems of young patients could play a role in age-related immunosenescence, T-cell dysfunction, and systemic inflammation.[125]

Age is crucial due to its impact on prognosis. Although study results are still inconsistent, some suggest worse outcomes in young age,[126,127] whereas others imply equal prognosis between young and old age[128] depending on the staging reported.[43,127] Contrary to other studies,[46,129,130] where stage III-IV cancer predominates in the young age group, we found more than half of our young patients with stage I-II cancer. However, our study reported no statistically significant difference in advanced disease between young and old patients, similar to a prior investigation.[131] This might reflect increased awareness of the disease among patients and primary care physicians, better access to colonoscopy, and more widespread use of CT with improved quality. Also, the introduction of national health insurance in the middle of the study period (2014) made access to healthcare more accessible, increasing people's concern for their health. Providing better facilities for cancer diagnosis may result in an inflation of the number of CRC and earlier detection of CRC through screening.[132] Cancer patients found through screening show up at a much earlier stage of the disease than those not found through screening. Our study found no distinct clinical characteristics between young and old patients regarding sex, side involvement, location, site, or specimen type. There is no tendency for proximalization of colon cancer in young patients compared to old patients in our study. Overall, the proximal and distal colon had an equal proportion of all CRC cases. However, if we included rectal cancer in the calculation of distal CRC, the proportion was in line with an extensive colonoscopy survey in Asia, which found that more patients had distal than proximal CRC.[133]

Single-institution and population-based studies have found that young patients with CRC have unique tumor locations, stages at presentation, and histologic features. Our findings were similar to those of these studies.[134–137] The proportion of rectal cancer among young patients was significantly higher than in their old counterparts; as previously mentioned in an American study, 32% of CRC occurred in the rectum.[137] Looking more specifically at colon subsites, young patients with CRC mainly have lesions originating from the ascending and descending colon. Meanwhile, the caecum, transverse colon, and sigmoid colon were the most affected sites among old populations. Lesions with poorly-defined histologic features, such as mucinous and signet ring features, are more likely associated with poor outcomes.[126] They are also more resistant to chemotherapy.[131] Our results showed that the proportion of adenocarcinoma NOS in young patients was less than in old patients, agreeing with a study by Chan et al[43] (84% vs. 92%) and Gheju et al[138] (86.7% vs. 84.7%). The mucinous histological variant was significantly higher in young than in old patients. Signet-ring cell cancer was only observed in young patients, accounting for only 0.6–1.0% of all CRC cases globally.[138] Our patient who has signet-ring cell cancer has the following characteristics: 48 years old, female, located in the caecum, right-sided, size 5.5 cm, brown-colored surface, exophytic, adequate LNR 5/13, pT3N2aM0 (IIIB), no LVI, no PNI, and with poor tumor differentiation. However, only one patient with signet-ring cell carcinoma was found in a Romanian study, and that patient was >50 years old.[138] Signet-ring cancers have intracellular mucin pushing the nucleus to one side and are associated with a more advanced stage at diagnosis, a higher incidence of LVI, LNM, and liver metastases, a higher

rate of recurrence, and higher aggression.[139,140] The literature stated that mucinous histopathology was a significant predictor of poor outcomes and more advanced node stage.[141]

The average number of dissected LNs in our study was lower than that in a recent Romanian study (9.96 ± 5.46 vs. 35.7 LNs removed), indicating that optimal LN sampling was a challenge in our institution.[138] Meanwhile, the average number of positive LNs per patient was lower than positive cases in Romania (1.54 ± 2.73 vs. 3.7 (1–62)).[138] The interpretation of LNM is thus more complicated because the number of dissected LNs was not ideal, but the positive number was satisfactory. More insufficiently removed LNs resulted in a higher probability of positive LNs in actual conditions due to unsuccessful LNs sampling, which could harm detection of cancer spread. This issue will have a significant impact on patient staging. In contrast, increasing the number of dissected LNs leads to more accurate information about node status and the best treatment for patients. In a recent Dutch nationwide study,[142] authors found that with an increasing number of evaluated nodes, the risk of mortality is decreased, related to a better quality of surgical resection (yielding more LN for the pathologist to assess).

A closer inspection of the dissected LNs in **Table 3** shows significant differences between the two age groups. The number of adequate LNs dissected in young patients was higher than in old patients, a favorable finding in young patients. Old patients are more likely to receive inadequate LN dissection during operative therapy. Old patients are at a higher surgical risk for various postoperative complications and have numerous comorbid diseases, possibly making surgeons consider the risks and benefits of a more thorough LN dissection.[143] The number of LNs dissected from resection specimens depends on several factors, including the surgeon's technique, bowel resection length, and tumor location.[144] The data supporting a minimal LN count of 12 is problematic, and a more realistic and practical LN count should be measured using LNR, a ratio of positive LNs to dissected LNs. Our average LNR was 0.18 ± 0.29, which was lower than a prior study in Romania (0.221 (0.139–1)),[138] which were more insufficient but had fewer positive LNs, presumably resulting in a lower class for LNR. LNR provides a superior prognostic power than the number of positive nodes alone and is significantly associated with poor survival of CRC.[145] However, given the absence of difference between the two age groups, it is advised that LNR be included as a predictive indicator in future CRC staging systems for all patients.

We found a lesser proportion of PNI in all patients compared to findings by Elsamany et al. [146] (11.3% vs. 24.4%). However, we found a higher proportion of PNI in young patients than in old patients, similar to a study by Zahir et al[45], showing that 22% of young patients with CRC had positive PNI. PNI is associated with a higher rate of metastatic disease, recurrence, and reduced survival. Several studies have recognized it as a notable independent prognostic factor in CRC multivariate analysis.[147]

Although some pathological features had significant differences between the two age groups, no evidence was found for significant differences in tumor size, growth pattern, tumor grade, pT, pN, LNR, LNM, distant metastasis, and LVI. Two-thirds of patients had tumor size ≥5 cm, the most significant size being 18 cm. Although some authors believe that tumor size does not affect prognosis, others believe that tumor size partially affects prognosis.[148,149] Increasing tumor size is associated with decreased loco-regional control, resulting in an increased risk of malignant potential.[150] Bigger tumors are more likely to be more invasive and invade neighboring organs.[151] Local recurrence was significantly higher in patients with tumors measuring ≥5 cm in size, poorly differentiated adenocarcinoma, pT4 stage, and having adjuvant radiotherapy. Moreover, the 5-year overall survival rates in patients with tumors ≥5 cm were lower than those with a size <5 cm (log-rank, p=0.001).[152]

According to our findings, the proportion of growth patterns was (from highest to lowest) exophytic in both age groups, endophytic, linitis plastica, and ulcerative. These findings agree with a previous study

in Thailand, which found that fungating and polyp mass (exophytic) were more common compared to ulcerative masses.[152] Our study demonstrated that the more common growth pattern is exophytic or polypoid growth (85.2%), which tends to be higher in old patients than in young patients (87.9% vs. 79.9%). Ulcerative growth and linitis plastica were much less common, which is favorable since both growth modes entail a worse prognosis. Linitis plastica suggests de novo origin, associated with a reduced proportion of KRAS mutations. Clinically, de novo tumors may represent a more aggressive subtype of CRC with a poorer prognosis, poorer disease progression, and higher aggressiveness.[107] These results call for more awareness and persistence in detecting non-polypoid lesions, more intensive monitoring of colonoscopically treated cases, and surgery for selected patients.

Concerning tumor grading, most tumors in both age categories were well-differentiated, similar to the results of a study from India.[141] These findings differed from those of a study by Chan et al[52], who discovered that both age groups were primarily affected by cases of moderately differentiated tumors. We found that young patients were more likely to have poorly differentiated CRC than old patients. This finding shows how young patients have predilections for more aggressive tumor biology and implies a poorer prognosis regarding distinct differentiation and histological subtypes distribution.[127,153] However, despite significant results in histological subtypes, we found no significant difference in tumor grade.

LVI was detected less frequently in our study (38.3%) compared to a previous report.[146] However, the proportion of positive LVI was higher in young patients than in old ones (41.7% vs. 36.7%). These results show that LVI is an important histopathological feature that needs to be evaluated in every young patient with CRC.

In short, all empirical findings related to clinicopathological characteristics of CRC in this study have provided a new understanding of this disease entity in Indonesia. Our study collected CRC data archived in one of Indonesia's national referral hospitals for cancer with a lengthy study period and the most robust data accessible in our nation. Its coverage could represent CRC epidemiology on a regional scale since primary data for the whole country is not readily available. Another strength of this study was that we applied an efficient and noteworthy statistical method called Joinpoint regression analysis to study the in-depth dynamics of CRC cases in Indonesia.[31,154,155] This approach has allowed estimation of the magnitude of incidences, testing the movement of cases statistically, and clearly illustrating the direction of CRC trends.[24,25,156] This study also provided several best-fitted models and computed forecasts that predict future trend patterns statistically.

However, our study should be interpreted with caution in light of the following limitations related to our research methodologies. As a retrospective study, the quality of our database depends on the patient records and is subjective to record bias. We also excluded patients from our study due to retention of medical records or microscopic slide deterioration. We may also have missed some old, frail patients with symptoms of CRC who were treated at home or in nursing homes without further investigation. Furthermore, several drawbacks might also arise concerning Joinpoint regression analysis to measure the trend of cases. This method's common impediment was that it only offered a description of the time series based solely on yearly aggregated data;[157] thus, it could not draw a causal relationship between possible risk factors that contributed to the findings.[158] As such, we could only hypothesize associations between CRC trends changes highlighted by our data and their possible influential factors supported by existing scientific evidence. Also, relying on the length of the study period, the software could only measure a certain number of year segments at a time.[156] A longer research term would have offered more freedom to measure the APC in several segmented sequences.[156] As a result, we could not compare several Joinpoint segments to gain additional clarity regarding the impact of a specific intervention or event. The analysis

could only be limited to 1 joinpoint because our samples only had 11 data points (i.e., 2009-2019).[156] To exemplify, given that Indonesia initially implemented universal health coverage in 2014, we might be unable to distinguish different APCs between 2009–2013 and 2014–2019.

In addition, the projections of future CRC incidence discussed in this study should be carefully interpreted.[112] Predictions of future cancer incidence inherently depend upon several uncertain factors, could be part of a larger cycle, and may not persist into the future. Our projection of CRC in 2020–2029 was assumed to have similar clinicopathological characteristics as the circumstances observed from 2009 to 2019. Any changes affecting future cancer incidence rates beyond those included in the model's base years could not be statistically calculated by the forecasting models.[159] Dynamic evolutions in the population (e.g., advancing obesity or smoking rates and introducing new screening programs with more cutting-edge technologies), governmental policy adjustments, and emerging public health threats (e.g., pandemics) may influence the record of a predictive number of cases.[159] Trends and projections could be volatile, and thus we could only forecast cases over a short period (e.g., ten years in our study) to maintain forecasting accuracy. Moreover, this work did not include population-level data, and the mathematical prediction of cases in this study should be further validated using multicenter data.[160] Therefore, population and multicenter epidemiological studies are highly suggested to further predict trends in this disease entity

Despite all methodology-related limitations, our data showed a similar trend to other countries worldwide, primarily Asian countries. The incidence rates fit well into forecasting models, allowing clinicians and policymakers to predict and anticipate future disease burdens of CRC.

Conclusion

This study sets out to assess clinical trends in CRC over 11 years based on tumor locations and side involvement, forecast the future incidence of CRC for the next ten years, and analyze the clinicopathological profile among Indonesian patients in a single center. Epidemiological trends and forecasting of CRC cases in Indonesian patients showed an enormous increase, notably for colon cancer, with a particularly concerning trend in young patients. Forecasts for the next ten years using fit-model regression analysis found a significantly high number of CRC burdens in the future, particularly for colon cancer compared to rectal cancer, which is stable and declining. Additionally, young patients exhibited particular clinicopathological characteristics regarding tumor location, tumor subsites, histological subtypes, adequacy of dissected LNs, and PNI, contributing to the disease's severity, aggressiveness, and prognosis. Multidisciplinary policies encompassing specialized screening protocols, extensive educational efforts, and lifestyle adjustments are required immediately to address this perplexing problem.

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Contributors

NR was the principal investigator of this study, conceptualized the study, acquired funding, accepted full responsibility for the work, and controlled the decision to publish. NR and MH did the investigation, designed the methodology, had full access to the data, contributed to the analysis, drafted the paper, and did the project administration. MH was entirely responsible for software utilization, data cleaning, and visualization of research findings. NR, MS, DRH, EK, MA, and WSJ collected the data, provided resources, and validated all data analyses. NR, EK, MA, and WSJ supervised the study process thoroughly. All authors

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Competing interests

None declared.

Patient consent for publication

General consent was obtained from the patient for the use of medical record data and residual specimens on admission, conforming with the ethics approval.

Ethics approval

This study did not involve the active participation of human subjects but employed medical records and biological materials stored as formalin-fixed paraffin-embedded (FFPE). It also has been approved by the Institutional Ethical Review Board (ERB) of the Faculty of Medicine, Universitas Indonesia - Dr. Cipto Mangkunkusumo Hospital, Jakarta, with the ethical approval number: KET-139/UN2.F1/ETIK/PPM.00.02/2020 and protocol number: 10-11-1416. The chart of cancer registry data was anonymized before the authors gained access to it for this study.

Provenance and peer review

Not commissioned; externally peer-reviewed.

Data availability statement

All data relevant to the study are included in the article.

Supplementary Information

- **Supplementary File 1. Trend Analysis of All Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement
- **Supplementary File 2. Trend Analysis of Young Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement
- **Supplementary File 3. Trend Analysis of Old Patients**
  Description: Detail analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among old patients based on tumor location and tumor side involvement
- **Supplementary File 4. Forecasting Analysis of All Patients**
  Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among all patients based on tumor location and tumor side involvement
- **Supplementary File 5. Forecasting Analysis of Young Patients**

Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among young patients based on tumor location and tumor side involvement

- **Supplementary File 6. Forecasting Analysis of Old Patients**
  Description: Detail analysis for forecasting future ten-years incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among old patients based on tumor location and tumor side involvement
- **Supplementary Table 1. Summary of Forecasted Cases 2020-2029**
  Description: Summary of a best-fitted model, predicted case equation, and number of forecasting cases during the period between 2020 and 2029

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Figure Legends

Figure 1. Study flow diagram for retrospective data collection, selection process, analysis of overall included samples, and subanalysis of complete data in the final report.

Figure 2. Trend analysis using Joinpoint regression expressed by annual percentage changes (APC) of colorectal cancer incidence among 1,584 patients during eleven years period of study classified by tumor locations (colorectal, colon, and rectum), and side involvement (right-sided and left-sided colorectal cancer) grouping in overall, young, and old patients. Colon plus rectum indicated a total incidence of both locations. A positive trend for 2009-2019 was observed among colorectal, colon, right-sided, and left-sided cancer, while rectal cancer tended to have stagnation and decrease in all young and old patients. Plotted lines indicate APCs. *indicates that the APC significantly differs from zero at the alpha = 0.05 level using the logarithmically transformed data permutation model in Joinpoint regression analysis.

Figure 3. Tumor subsites specific incidence rate using Joinpoint regression expressed by annual percentage changes (APC) of colorectal cancer incidence among 1,584 patients during 2009-2019 based on anatomical subsites of tumor in the colon in all patients. A sharp increase of cases by order in value was found in ascending, descending, transverse, and sigmoid colon, respectively, while a gradual decline was observed in the caecum. *denotes a significant change in APC versus 0 (P <0·050) using the logarithmically transformed data permutation model in Joinpoint regression analysis.

Figure 4. Annual incidence trends, the equation for predicting cases, and the forecast number of cases in the next-ten year using the best fitted-model regression analysis (linear, quadratic, exponential growth, or S-shaped curve model) for colorectal cancer classified by tumor locations (colorectal, colon, and rectum), and side involvement (right-sided and left-sided colorectal cancer) grouping by in all, young, and old patients. Projection of a positive trend for the period 2020-2029 is observed among colorectal, colon, and left-sided cancer, while rectal cancer tended to have stagnation and decrease in all, young, and old patients. Right-sided colorectal cancer was forecasted to have an increased burden in overall and old patients but

tended to decrease in young patients. * indicates significant progression slope ($p<0.05$; ANOVA statistical test); Blue connected points show actual rates, red loosely dotted connected line indicate a best-fitted trend, and the green densely connected dotted line indicates the forecasting trend. Y_t is the variable (equation for predicted cases), and t is the time unit (year) value. **Abbreviations**: CRC, colorectal cancer; MAPE, mean absolute percent error; MAD, mean absolute deviation; MSD, mean square deviation.

Figure 5. Histopathological features of colorectal cancer resection specimen (all in HE staining). (a) well-differentiated adenocarcinoma NOS (M40x); (b) poorly differentiated adenocarcinoma NOS (M40x); (c) mucinous adenocarcinoma (M40x, inlet 100x); (d) signet-ring cell carcinoma (M40x, inlet 400x); (e) pT2 stage tumor infiltrating muscular layer (M40x); (f) pT3 stage tumor infiltrating adipose tissue in subserosal layer (M40x); (g) lymphovascular invasion (pointed by red arrow, M40x); (h) perineural invasion (highlighted by yellow arrow, M40x); (i) lymph node metastasis (M100x).

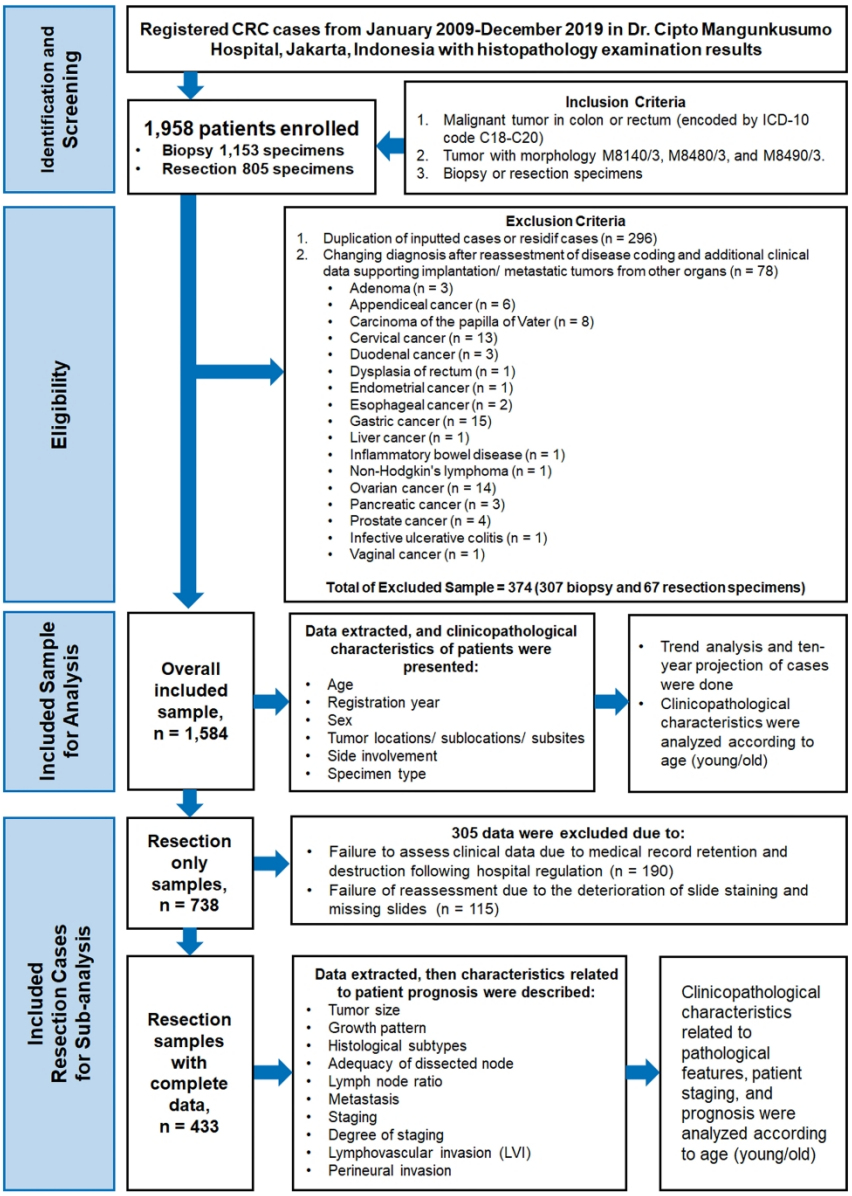

Figure 1. Study flow diagram for retrospective data collection, selection process, analysis of overall included samples, and subanalysis of complete data in the final report.

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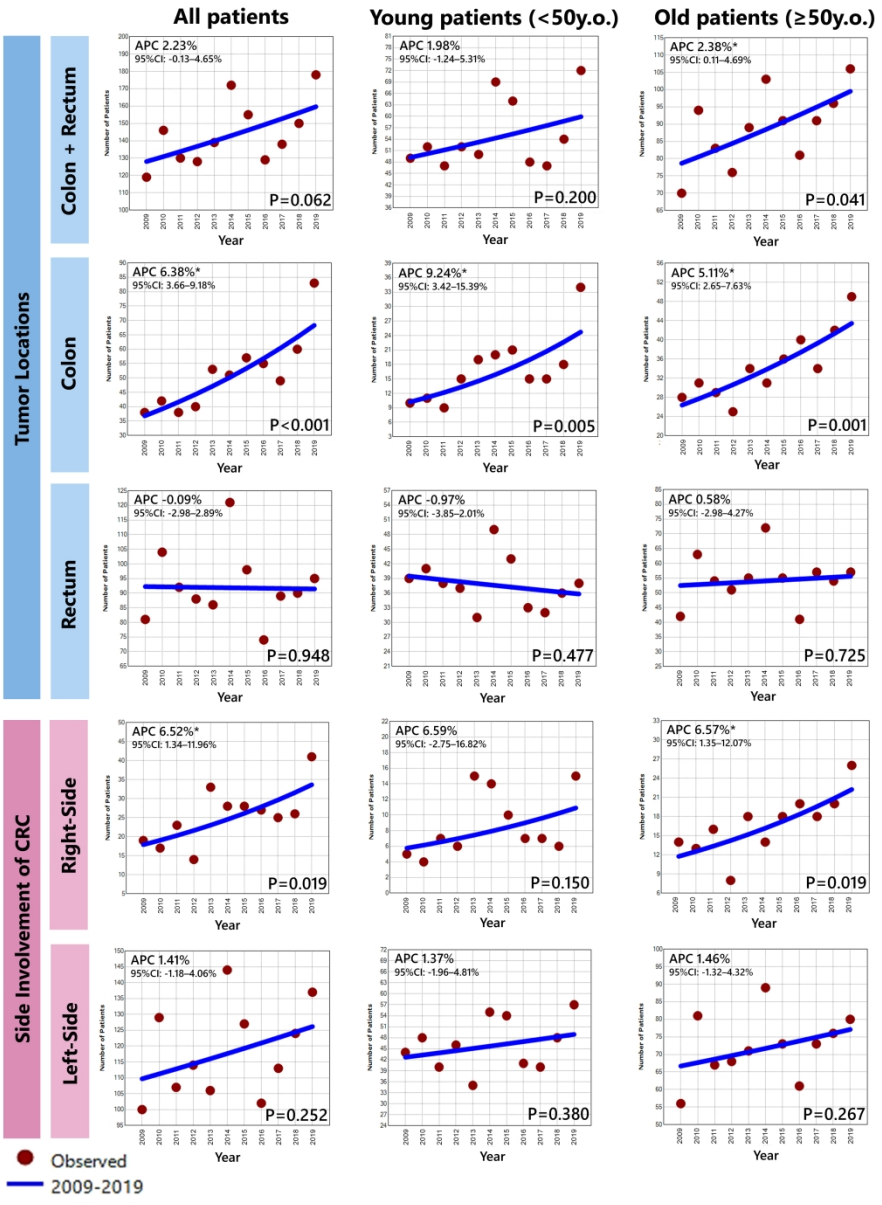

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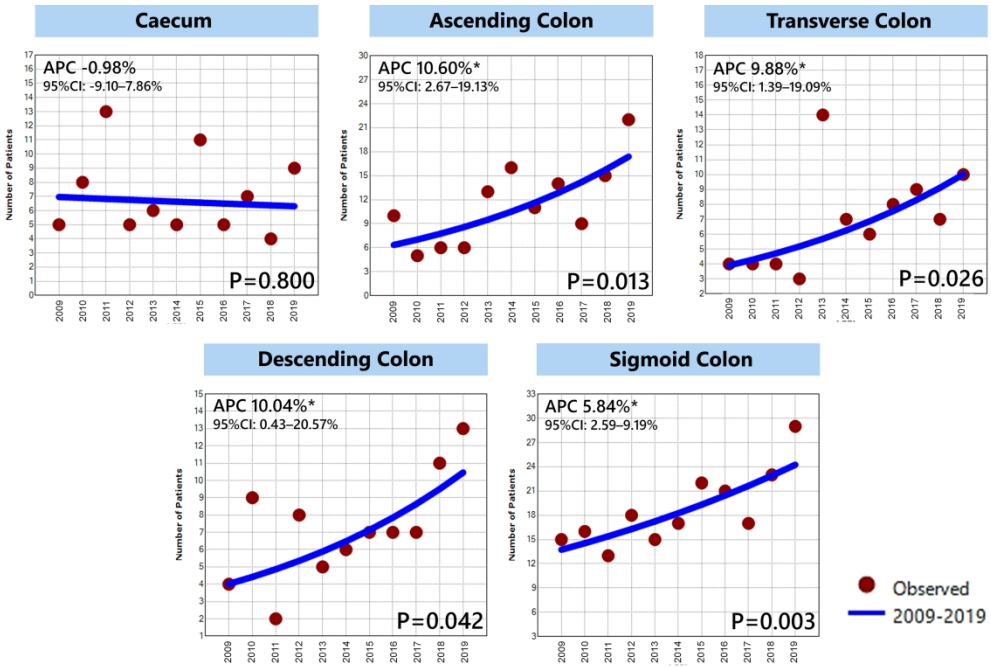

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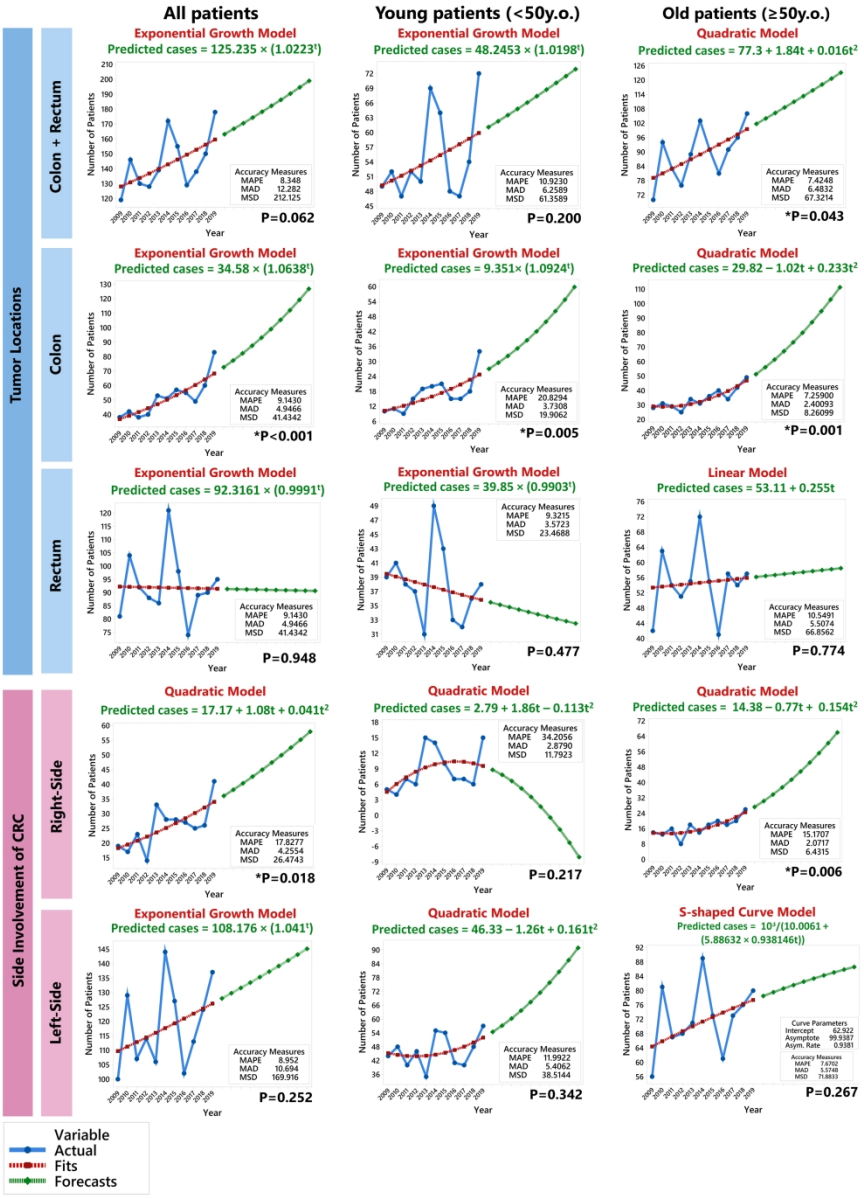


Figure 4. Annual incidence trends, the equation for predicting cases, and the forecast number of cases in the next-ten year using the best fitted-model regression analysis (linear, quadratic, exponential growth, or S-shaped curve model) for colorectal cancer classified by tumor locations (colorectal, colon, and rectum), and side involvement (right-sided and left-sided colorectal cancer) grouping by in all, young, and old patients. Projection of a positive trend for the period 2020-2029 is observed among colorectal, colon, and left-sided cancer, while rectal cancer tended to have stagnation and decrease in all, young, and old patients. Right-sided colorectal cancer was forecasted to have an increased burden in overall and old patients but tended to decrease in young patients. * indicates significant progression slope ($p<0.05$; ANOVA statistical test); Blue connected points show actual rates, red loosely dotted connected line indicate a best-fitted trend, and the green densely connected dotted line indicates the forecasting trend. Yt is the variable (equation for predicted cases), and t is the time unit (year) value. **Abbreviations:** CRC, colorectal cancer; MAPE, mean absolute percent error; MAD, mean absolute deviation; MSD, mean square deviation.

163x222mm (600 x 600 DPI)

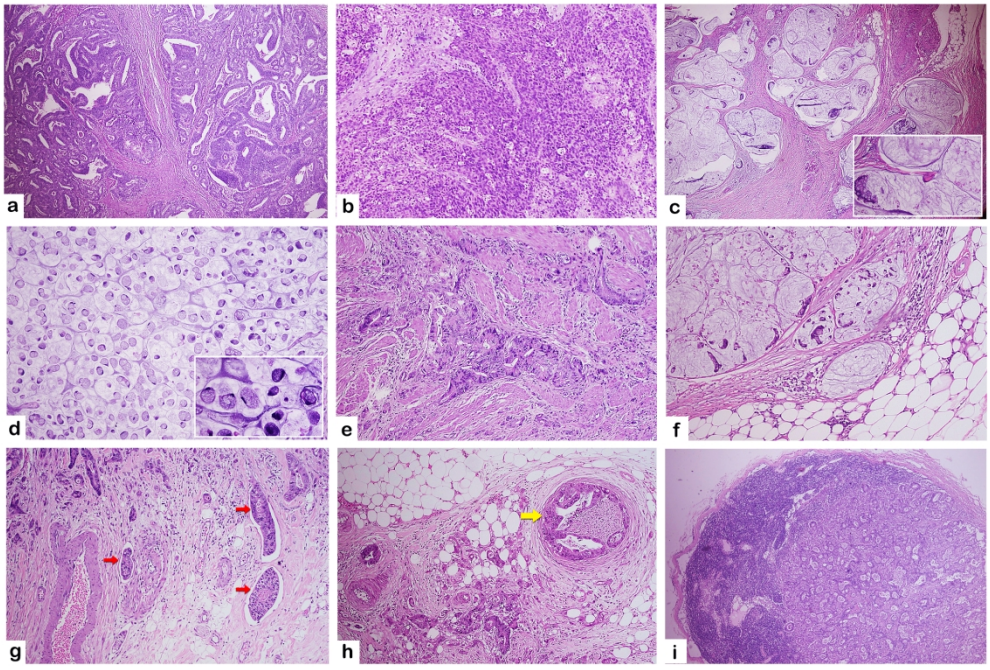


Figure 5. Histopathological features of colorectal cancer resection specimen (all in HE staining). (a) well-differentiated adenocarcinoma NOS (M40x); (b) poorly differentiated adenocarcinoma NOS (M40x); (c) mucinous adenocarcinoma (M40x, inlet 100x); (d) signet-ring cell carcinoma (M40x, inlet 400x); (e) pT2 stage tumor infiltrating muscular layer (M40x); (f) pT3 stage tumor infiltrating adipose tissue in subserosal layer (M40x); (g) lymphovascular invasion (pointed by red arrow, M40x); (h) perineural invasion (highlighted by yellow arrow, M40x); (i) lymph node metastasis (M100x).

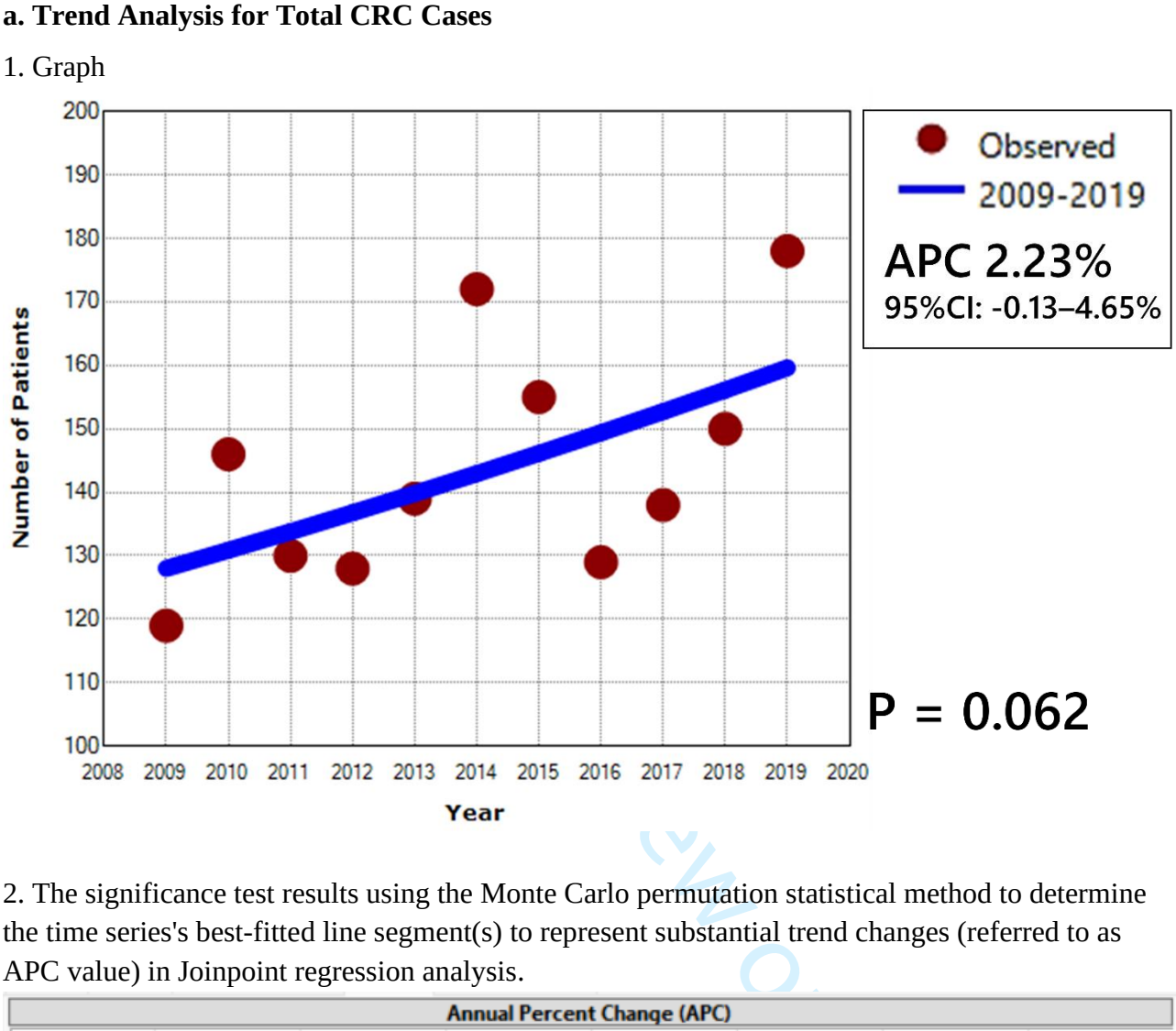
188x127mm (300 x 300 DPI)

Supplementary File 1.

Detailed analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among all patients based on tumor location and tumor side involvement.

a. Trend Analysis for Total CRC Cases

1. Graph

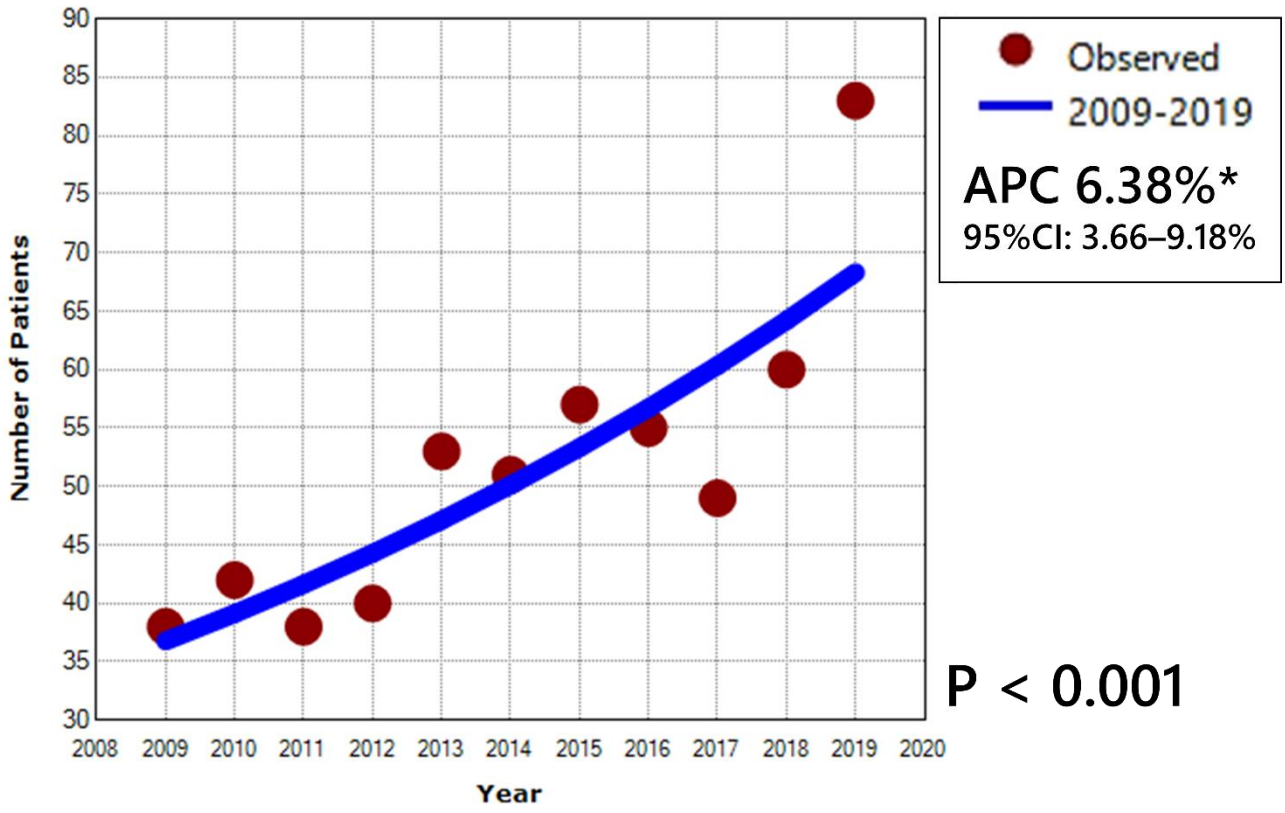


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	2.23	-0.13	4.65	2.13	0.062
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	2.23	-0.13	4.65	2.13	0.062
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Total Colon Cancer Cases

1. Graph

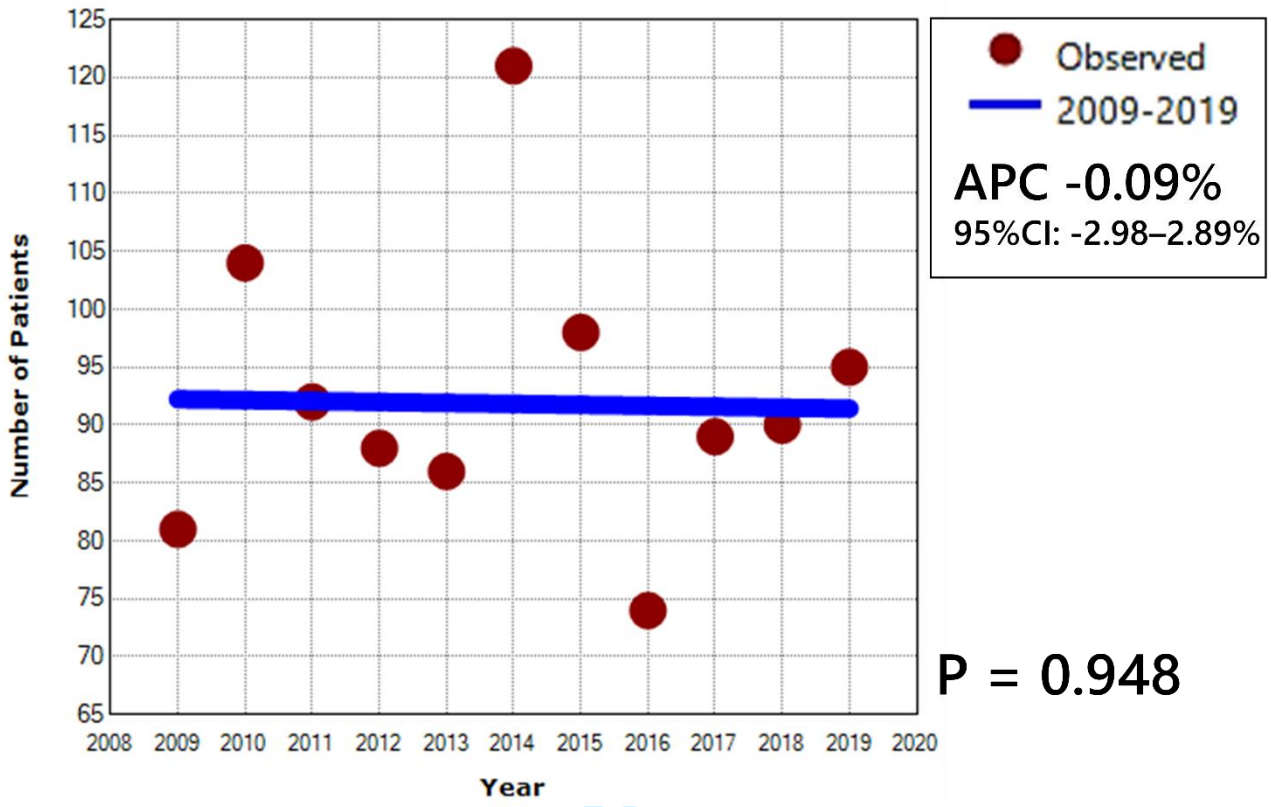


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.38*	3.66	9.18	5.39	< 0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.38*	3.66	9.18	5.39	< 0.001
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Total Rectal Cancer Cases

1. Graph

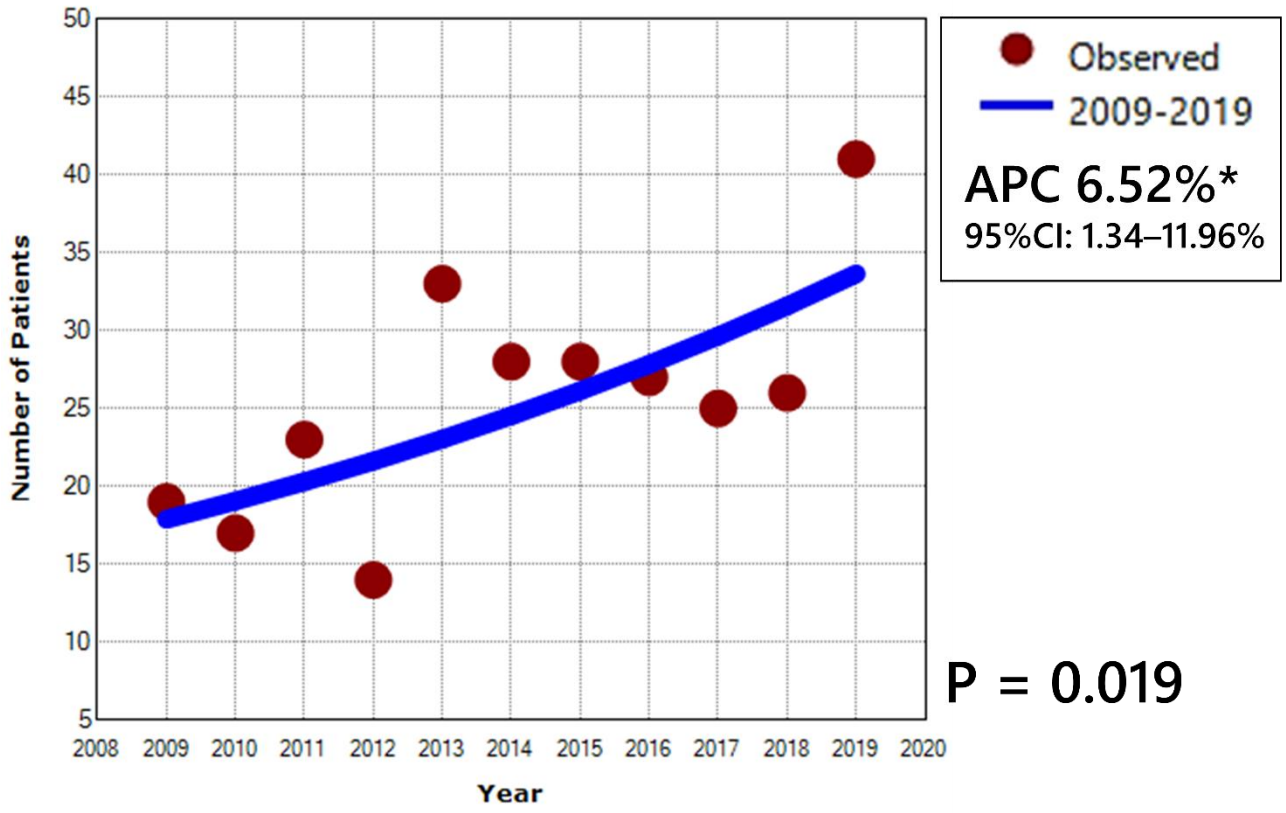


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.09	-2.98	2.89	-0.07	0.948
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.09	-2.98	2.89	-0.07	0.948
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Total Right-Sided CRC Cases

1. Graph

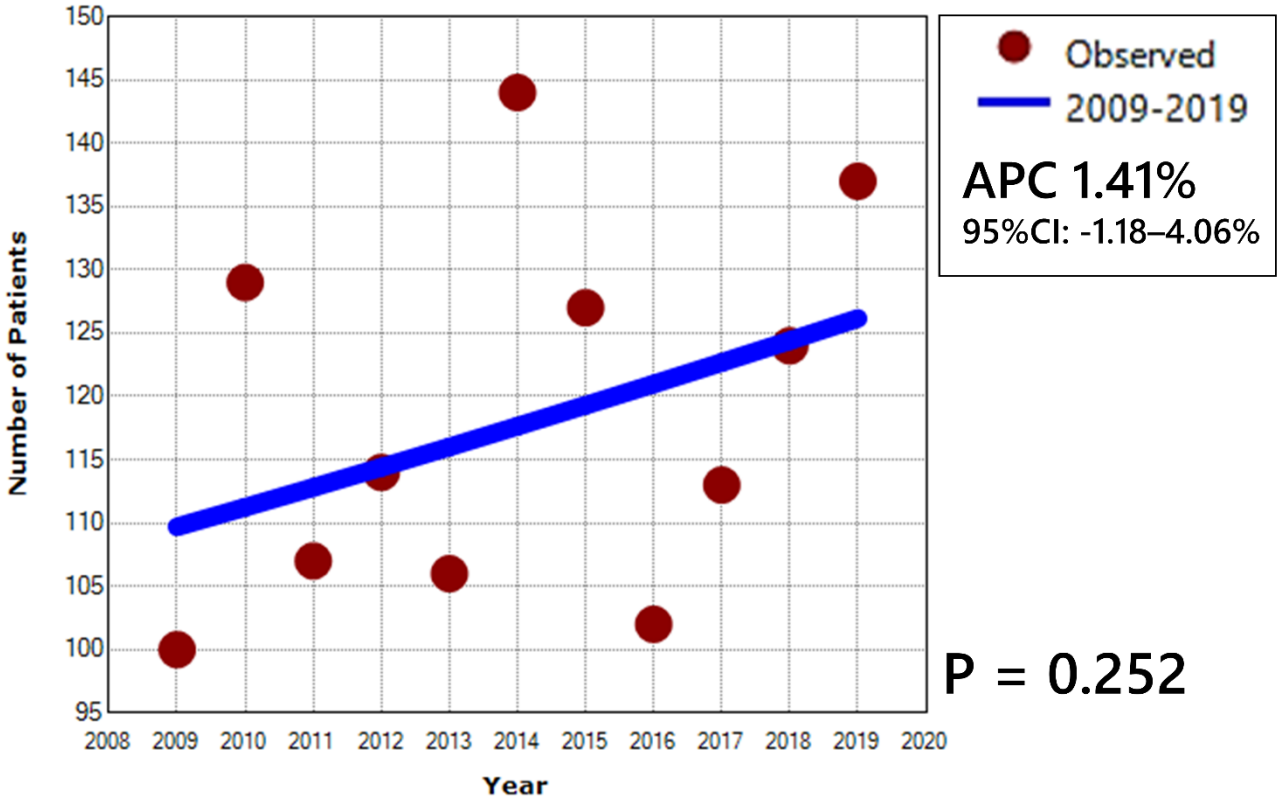


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.52*	1.34	11.96	2.87	0.019
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.52*	1.34	11.96	2.87	0.019
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Total Left-Sided CRC Cases

1. Graph

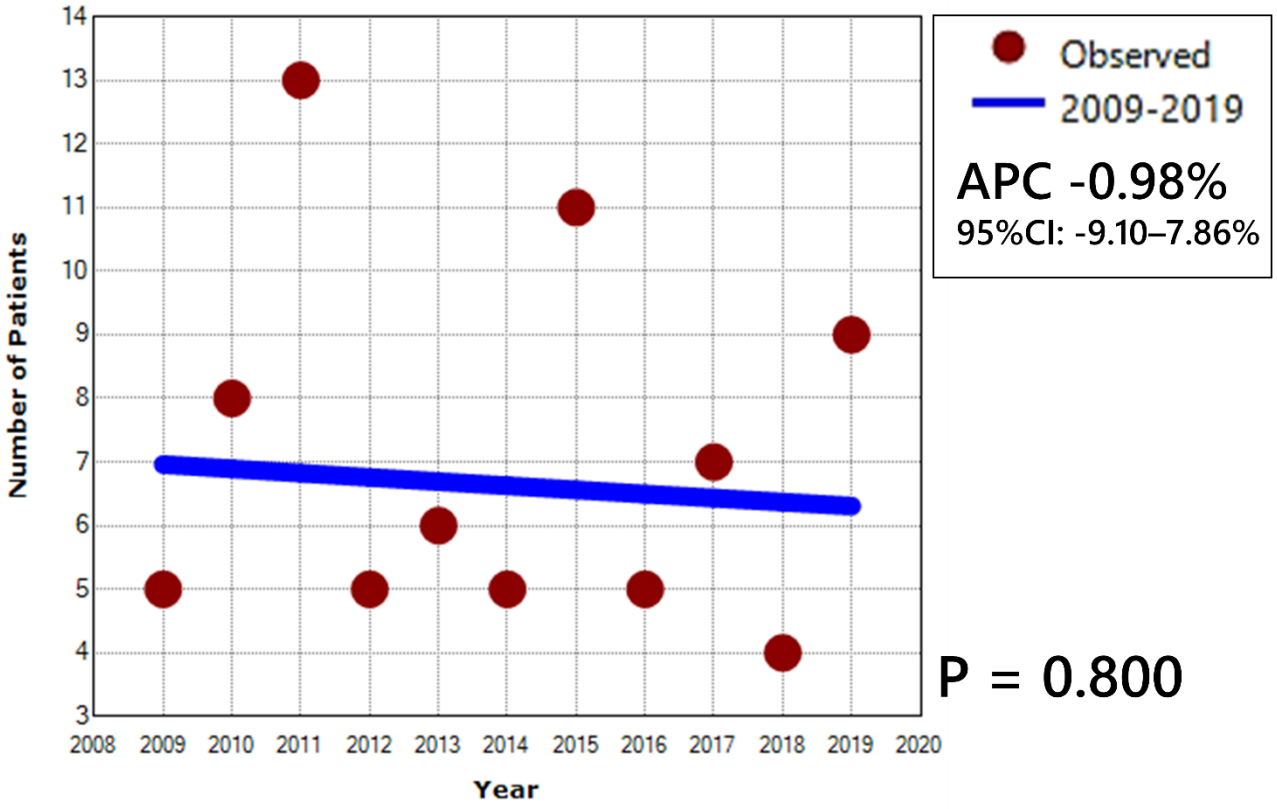


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.41	-1.18	4.06	1.23	0.252
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.41	-1.18	4.06	1.23	0.252
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

f. Trend Analysis for Total CRC Cases Originated from Caecum

1. Graph

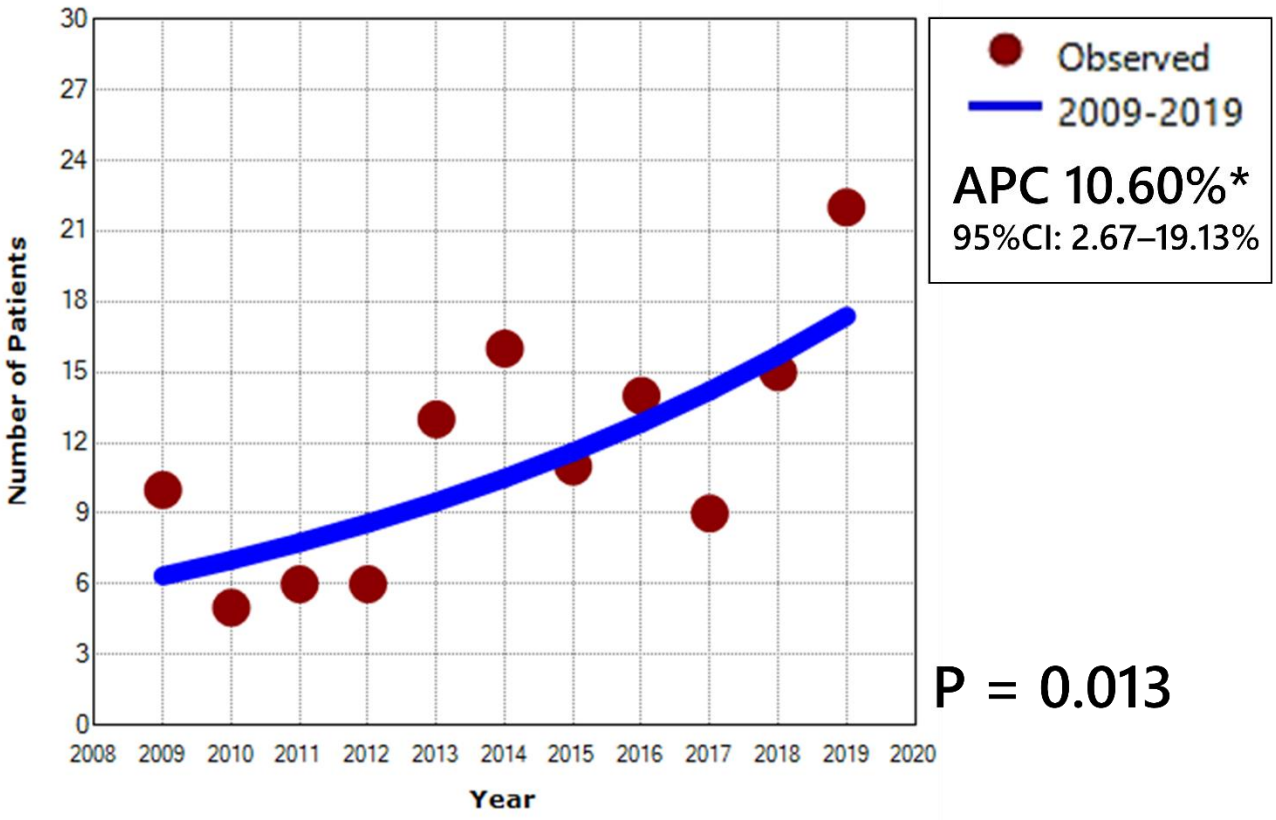


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.98	-9.10	7.86	-0.26	0.800
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.98	-9.10	7.86	-0.26	0.800
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

g. Trend Analysis for Total CRC Cases Originated from Ascending Colon

1. Graph

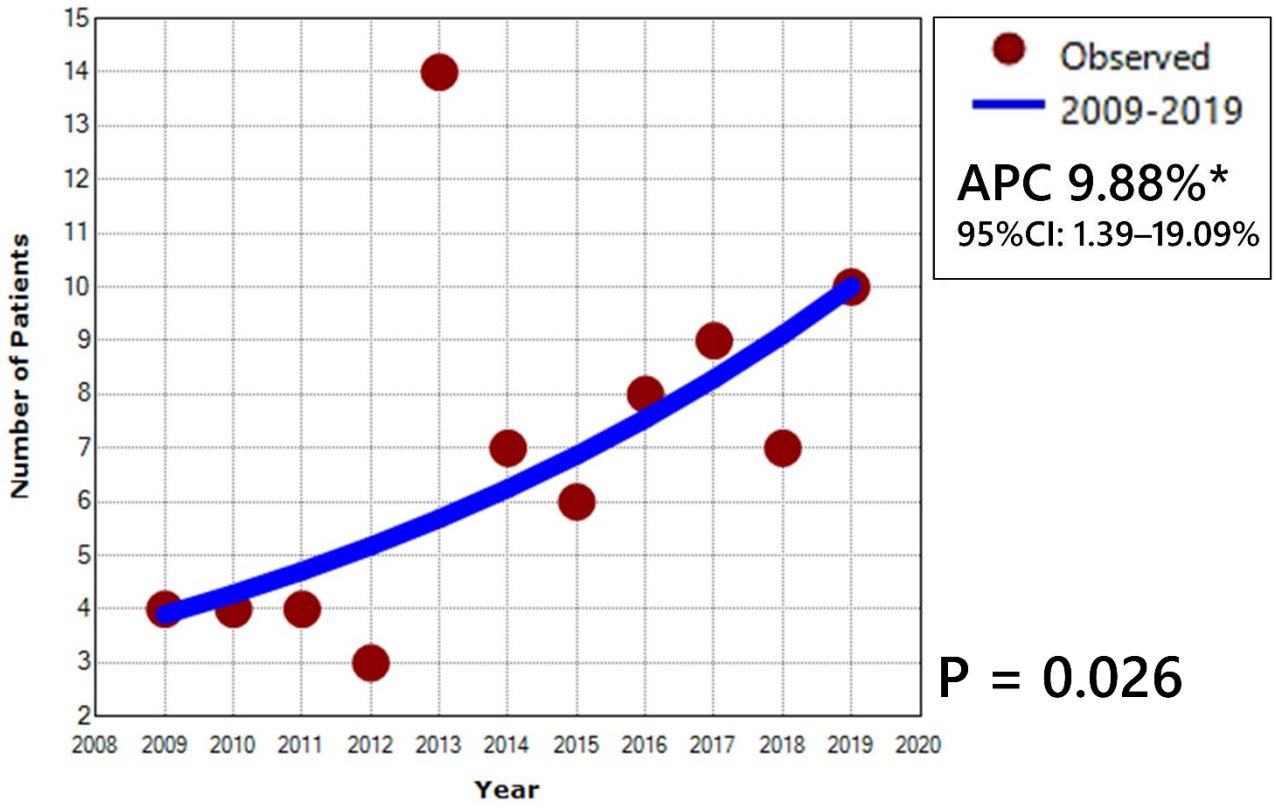


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	10.60*	2.67	19.13	3.07	0.013
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	10.60*	2.67	19.13	3.07	0.013
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

h. Trend Analysis for Total CRC Cases Originated from Transverse Colon

1. Graph

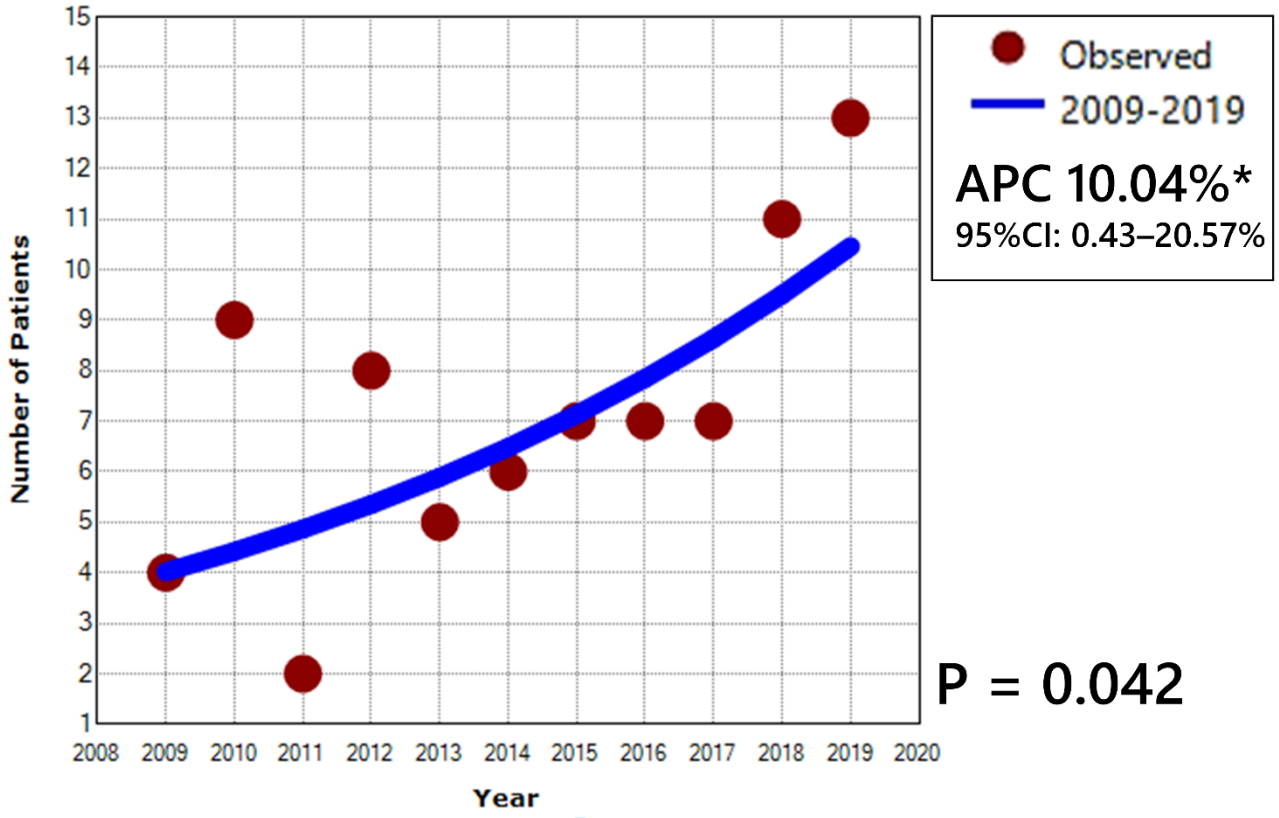


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	9.88*	1.39	19.09	2.65	0.026
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	9.88*	1.39	19.09	2.65	0.026
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

i. Trend Analysis for Total CRC Cases Originated from Descending Colon

1. Graph

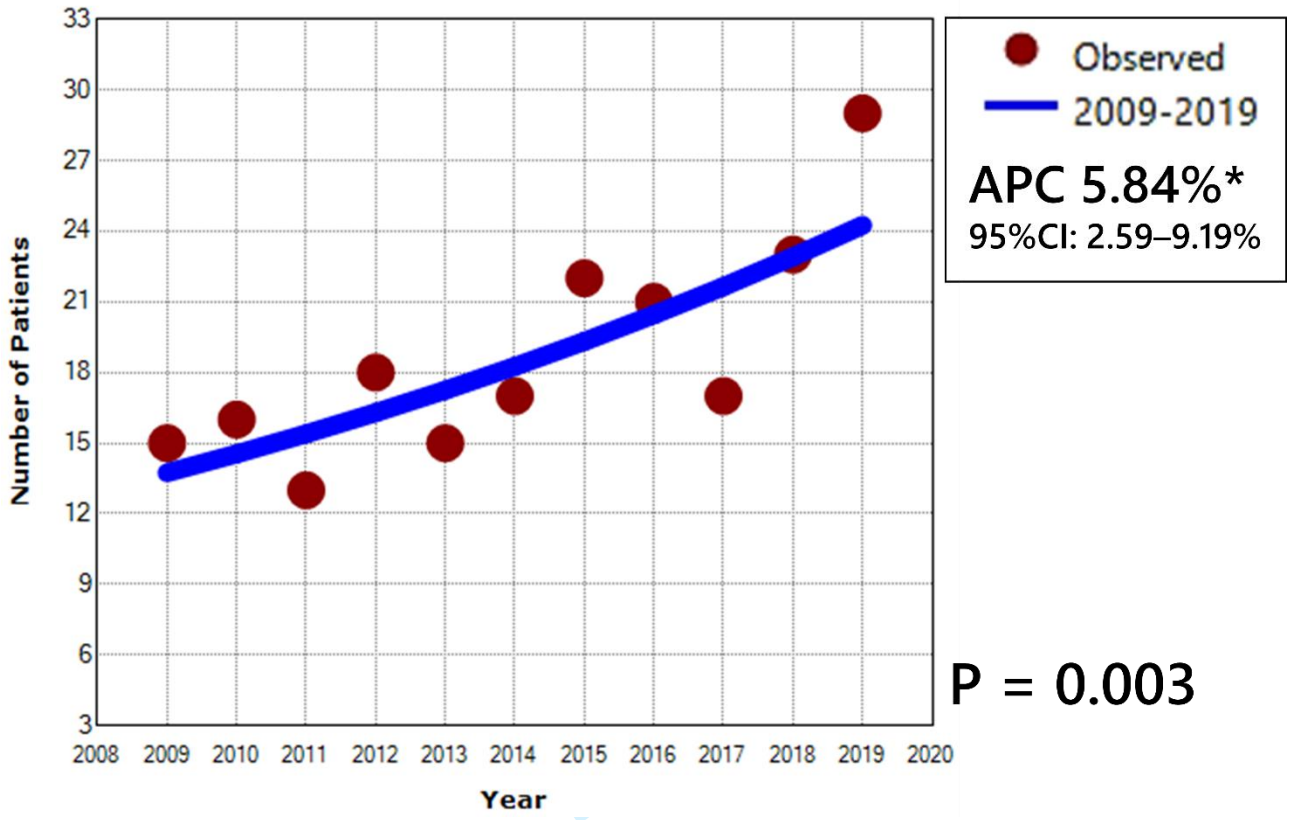


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	10.04*	0.43	20.57	2.37	0.042
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	10.04*	0.43	20.57	2.37	0.042
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

j. Trend Analysis for Total CRC Cases Originated from Sigmoid

1. Graph



2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

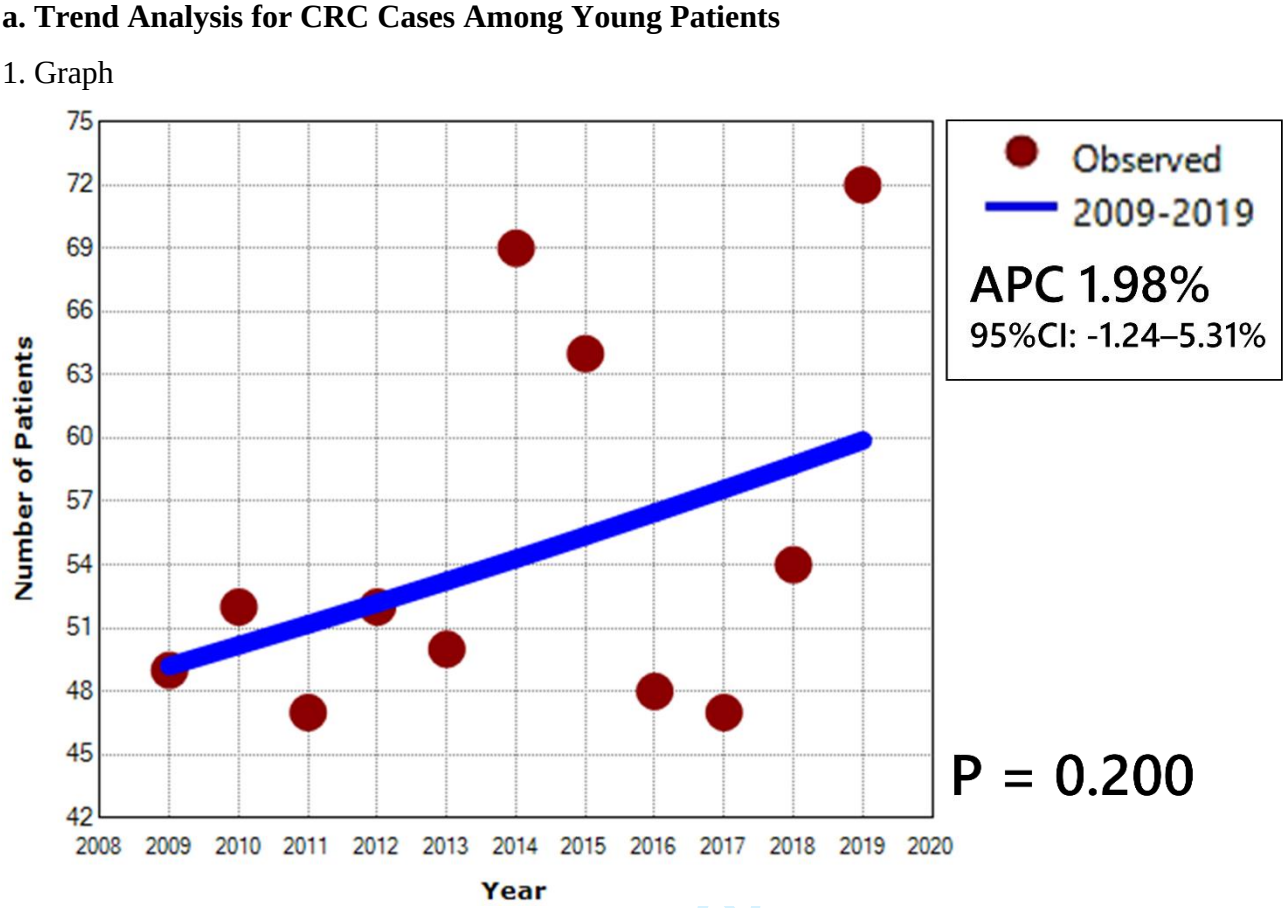
Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	5.84*	2.59	9.19	4.12	0.003
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	5.84*	2.59	9.19	4.12	0.003
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

Supplementary File 2.

Detailed analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among young patients based on tumor location and tumor side involvement

a. Trend Analysis for CRC Cases Among Young Patients

1. Graph

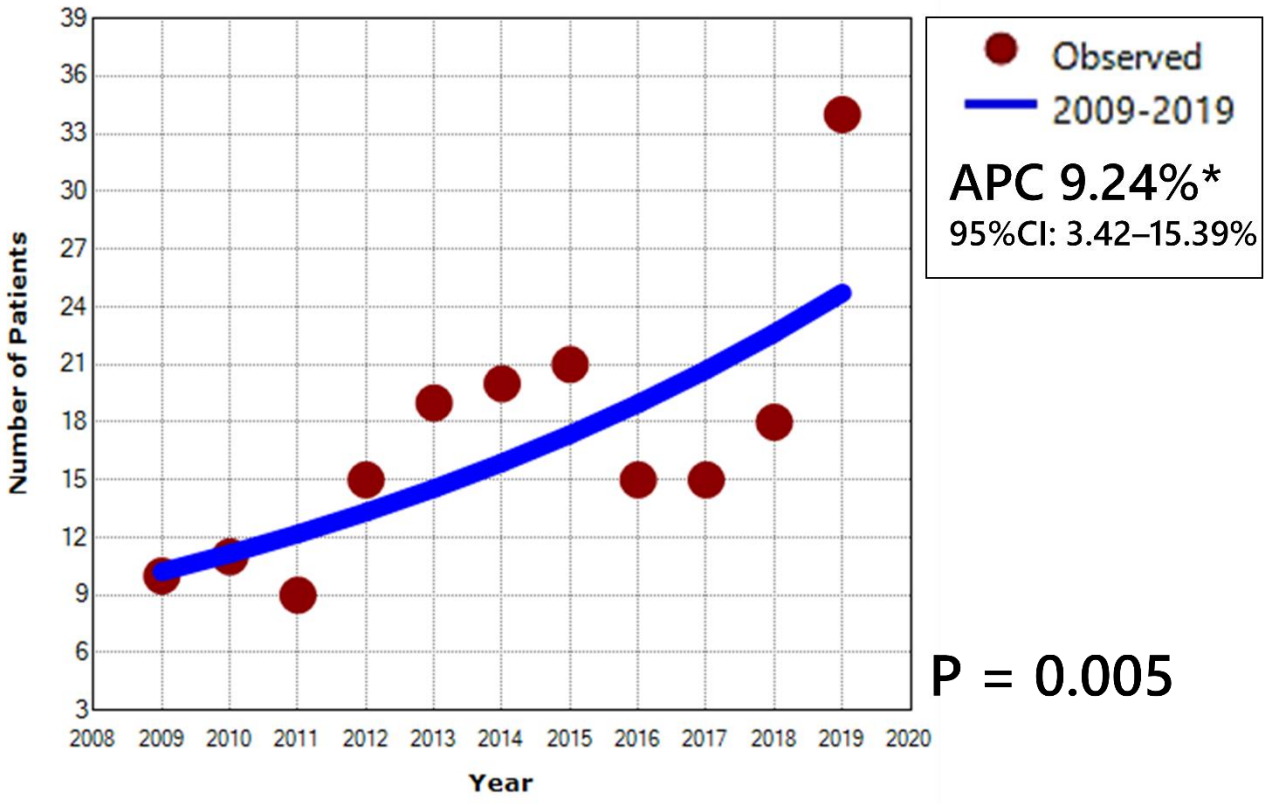


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.98	-1.24	5.31	1.38	0.200
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.98	-1.24	5.31	1.38	0.200
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Colon Cancer Cases Among Young Patients

1. Graph

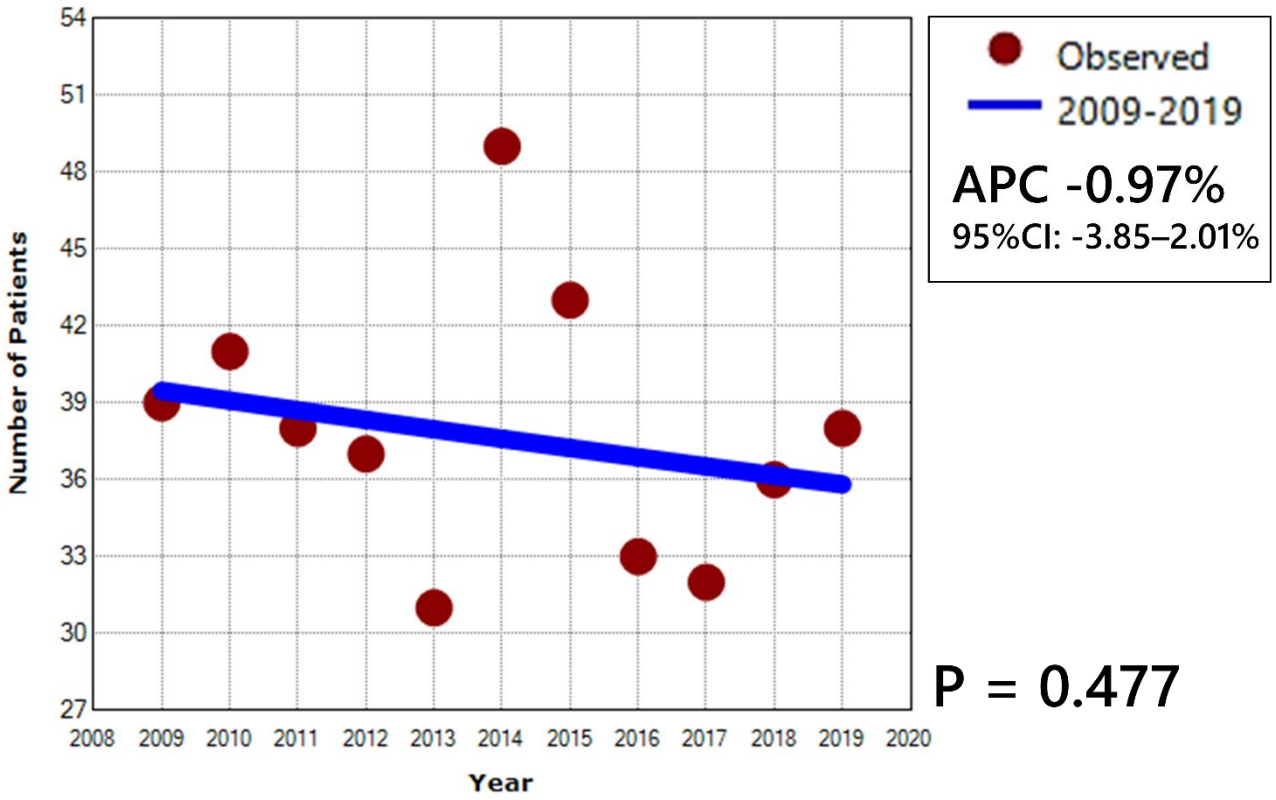


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	9.24*	3.42	15.39	3.65	0.005
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	9.24*	3.42	15.39	3.65	0.005
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Rectal Cancer Cases Among Young Patients

1. Graph

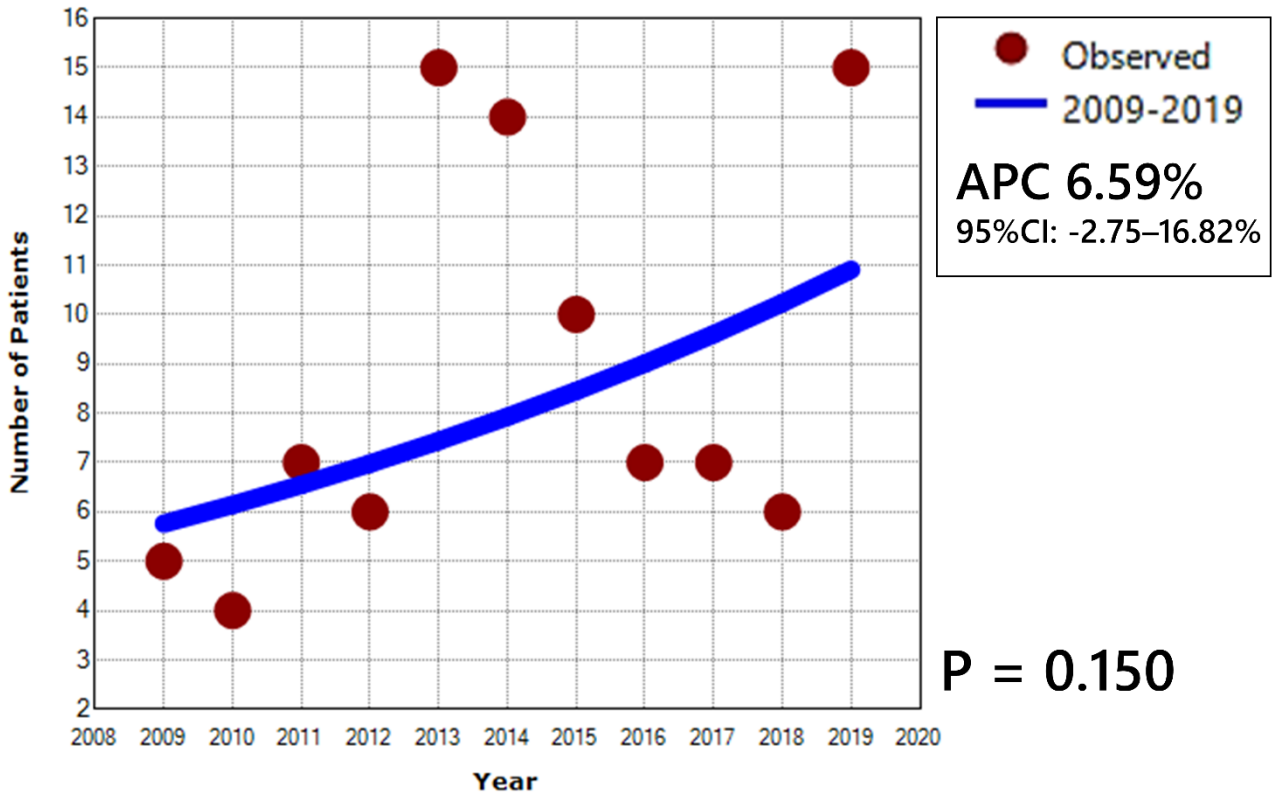


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	-0.97	-3.85	2.01	-0.74	0.477
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	-0.97	-3.85	2.01	-0.74	0.477
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Right-Sided CRC Cases Among Young Patients

1. Graph

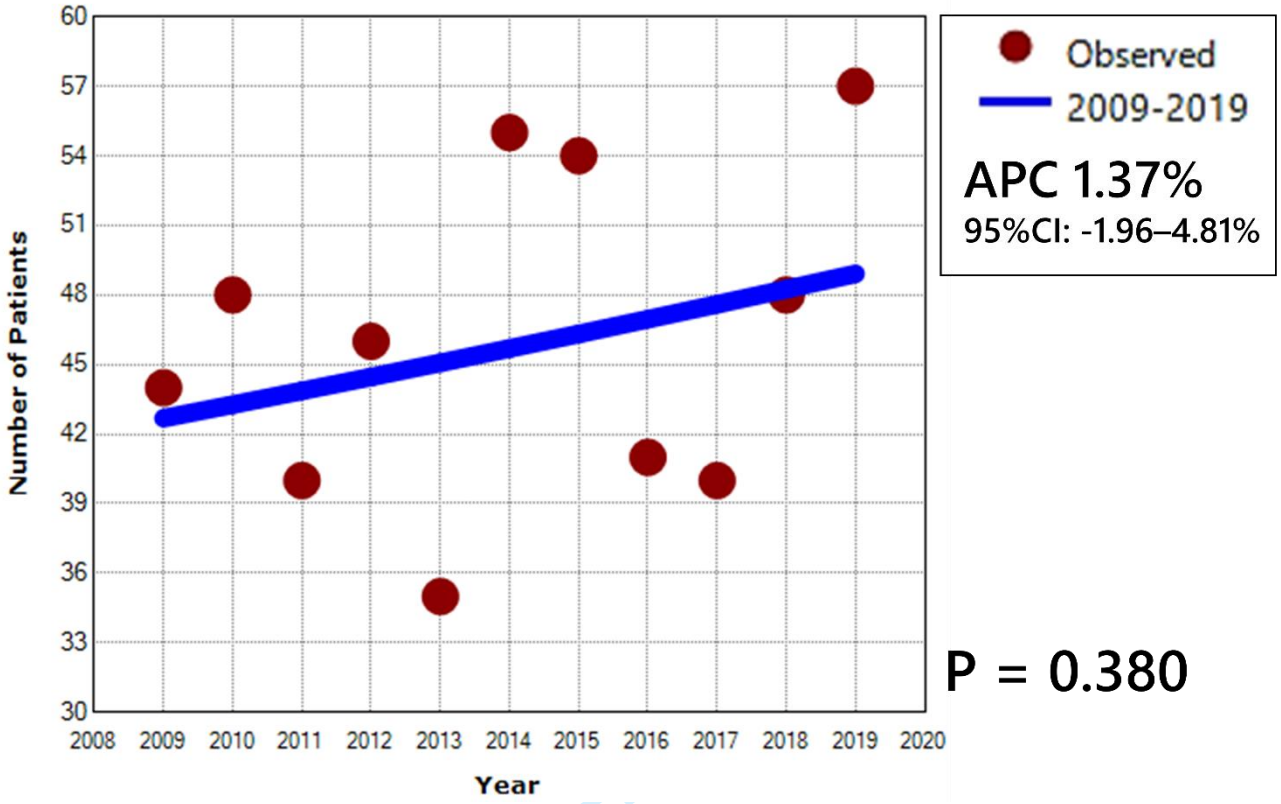


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.59	-2.75	16.82	1.57	0.150
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.59	-2.75	16.82	1.57	0.150
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Left-Sided CRC Cases Among Young Patients

1. Graph



2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis.

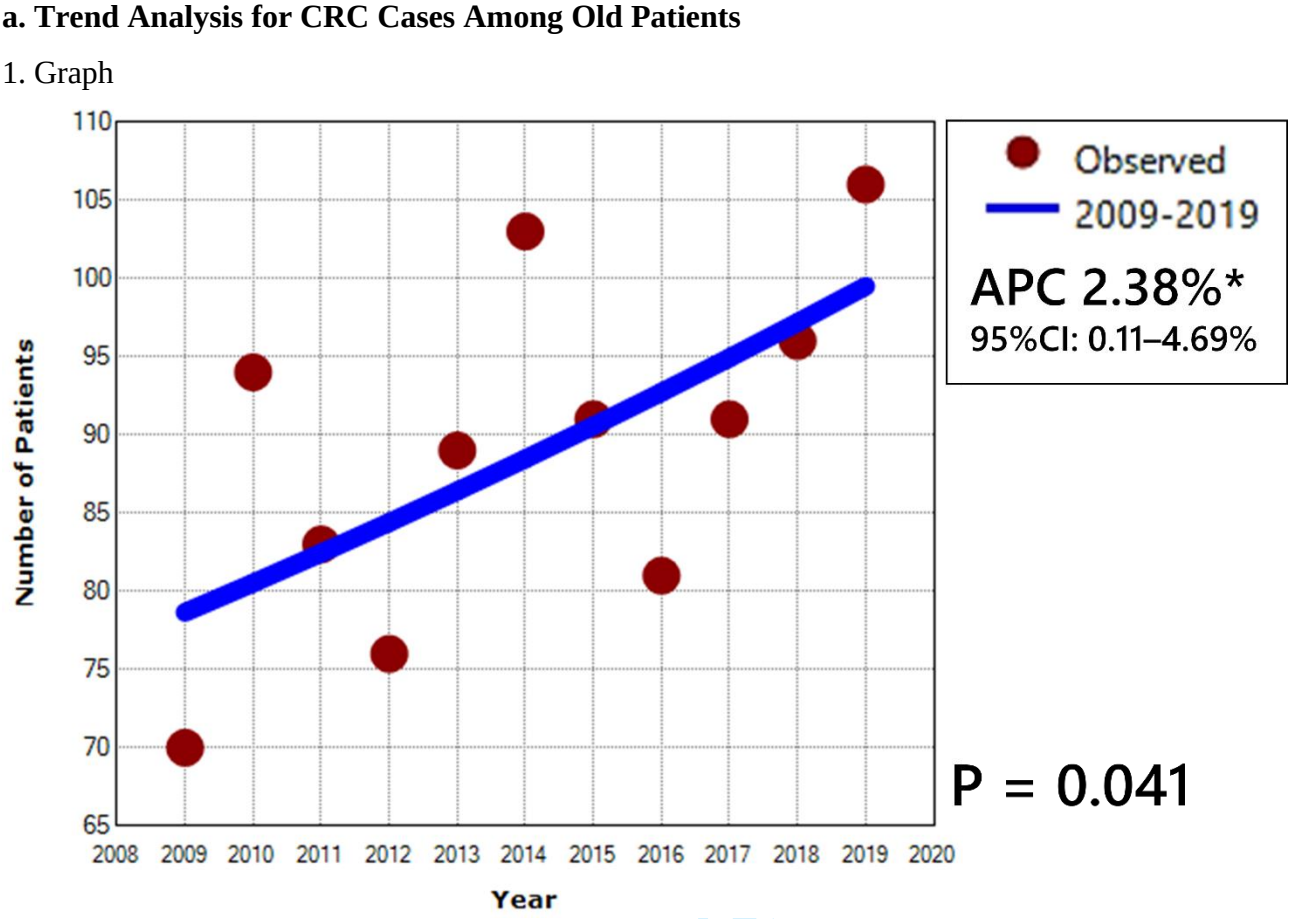
Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.37	-1.96	4.81	0.92	0.380
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.37	-1.96	4.81	0.92	0.380
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

Supplementary File 3.

Detailed analysis of annual incidence trend of colorectal cancer using Joinpoint regression analysis among old patients based on tumor location and tumor side involvement

a. Trend Analysis for CRC Cases Among Old Patients

1. Graph

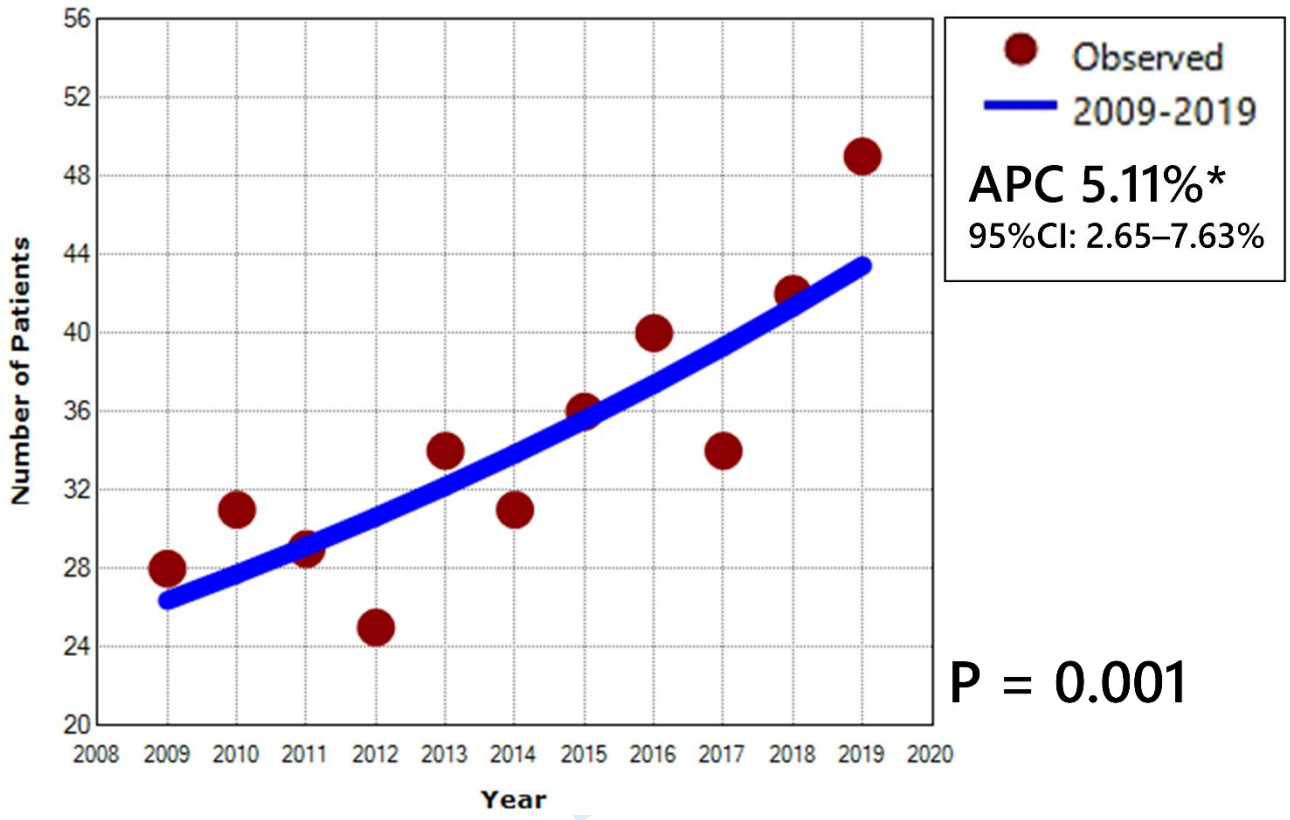


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	2.38*	0.11	4.69	2.38	0.041
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	2.38*	0.11	4.69	2.38	0.041
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

b. Trend Analysis for Colon Cancer Cases Among Old Patients

1. Graph

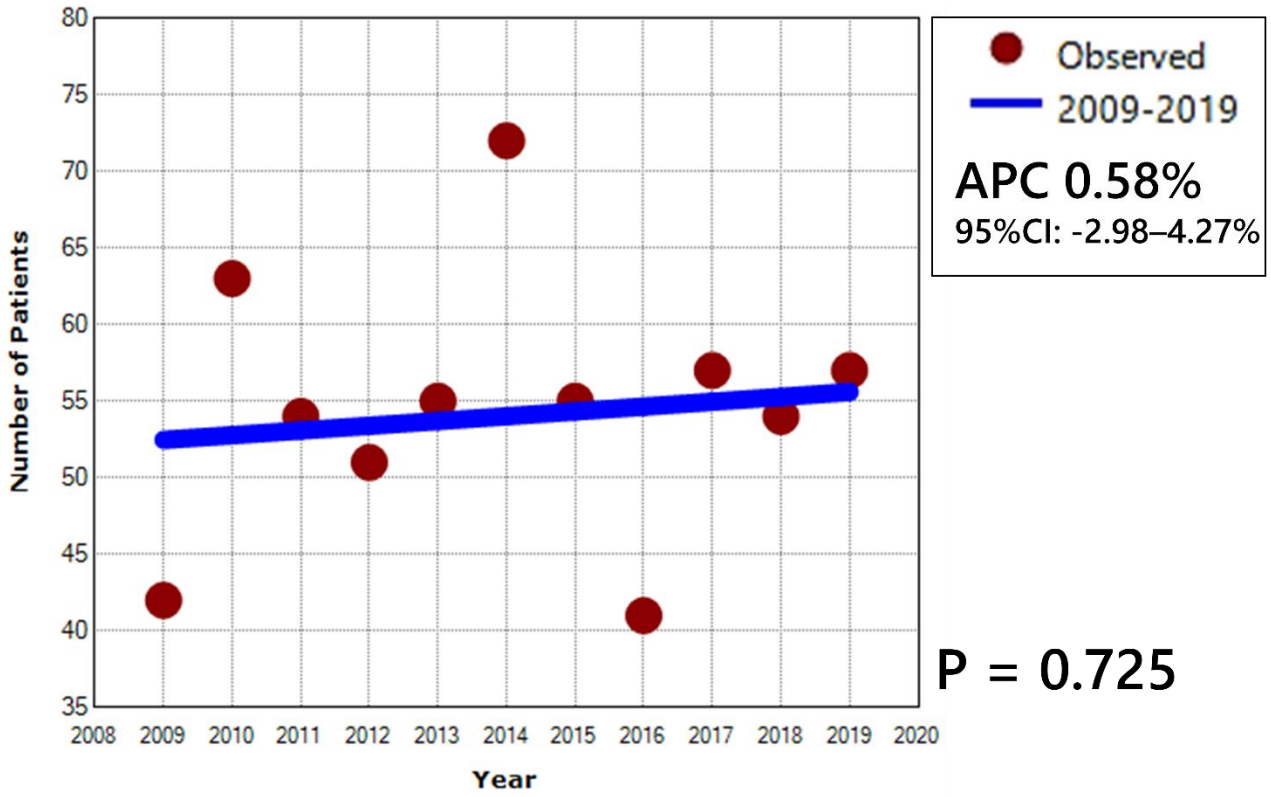


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	5.11*	2.65	7.63	4.76	0.001
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	5.11*	2.65	7.63	4.76	0.001
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

c. Trend Analysis for Rectal Cancer Cases Among Old Patients

1. Graph

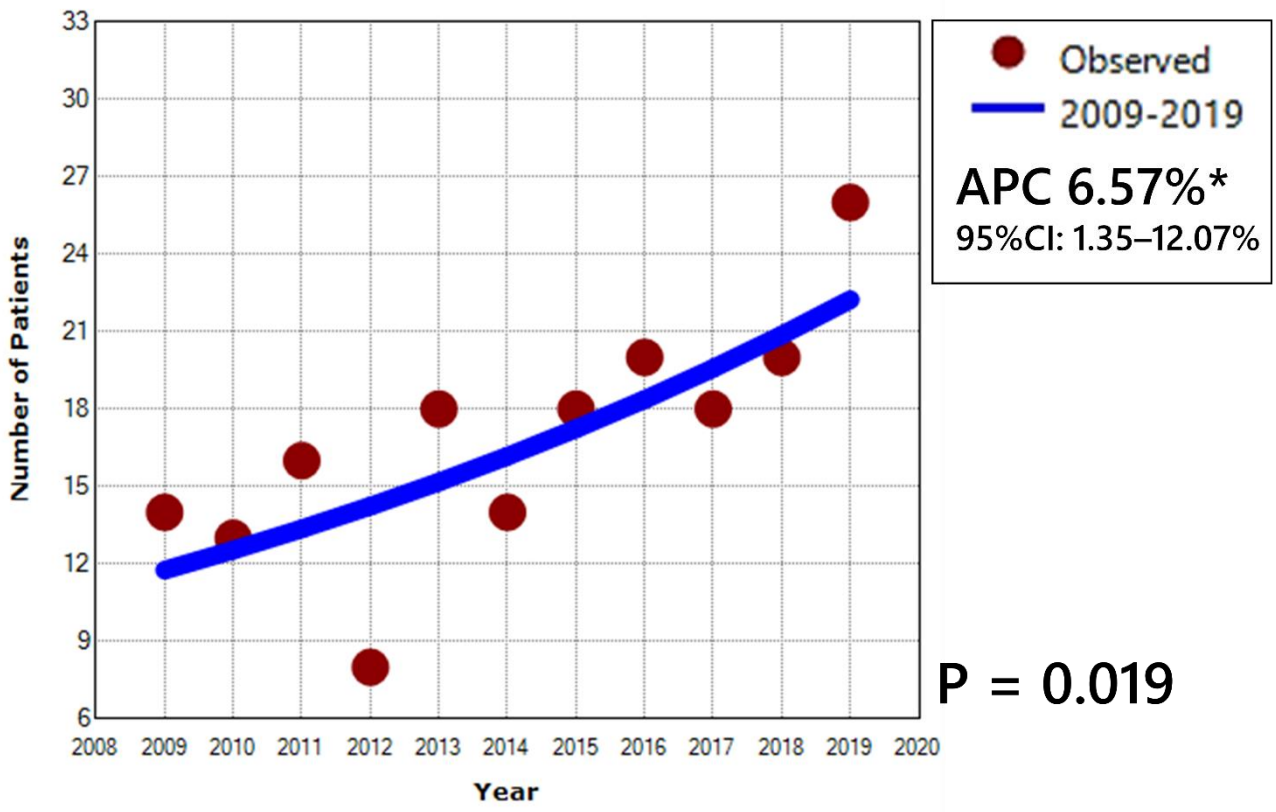


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	0.58	-2.98	4.27	0.36	0.725
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	0.58	-2.98	4.27	0.36	0.725
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

d. Trend Analysis for Right-Sided CRC Cases Among Old Patients

1. Graph

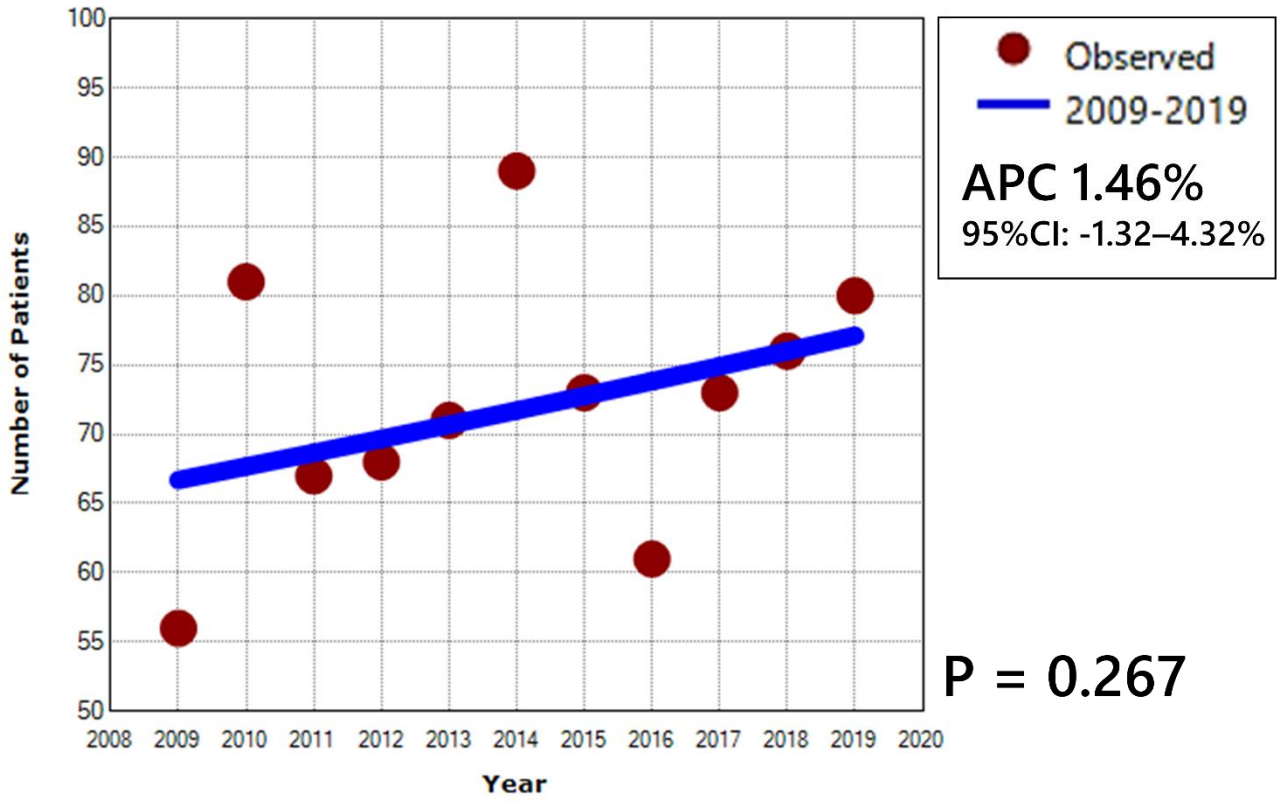


2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis:

Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	6.57*	1.35	12.07	2.87	0.019
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	6.57*	1.35	12.07	2.87	0.019
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

e. Trend Analysis for Left-Sided CRC Cases Among Old Patients

1. Graph



2. The significance test results using the Monte Carlo permutation statistical method to determine the time series's best-fitted line segment(s) to represent substantial trend changes (referred to as APC value) in Joinpoint regression analysis:

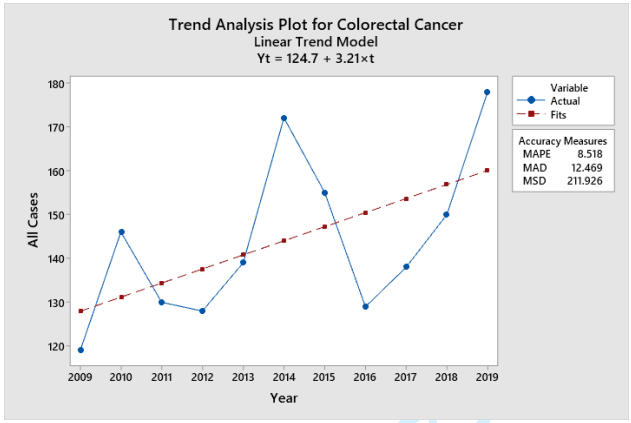
Annual Percent Change (APC)							
Segment	Lower Endpoint	Upper Endpoint	APC	Lower CI	Upper CI	Test Statistic (t)	Prob > |t|
1	2009.00	2019.00	1.46	-1.32	4.32	1.18	0.267
* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level							
Average Annual Percent Change (AAPC)							
Range	Lower Endpoint	Upper Endpoint	AAPC	Lower CI	Upper CI	Test Statistic~	P-Value~
Full Range	2009.00	2019.00	1.46	-1.32	4.32	1.18	0.267
* Indicates that the AAPC is significantly different from zero at the alpha = 0.05 level. ~ If the AAPC is within one segment, the t-distribution is used. Otherwise, the normal (z) distribution is used. Learn More							

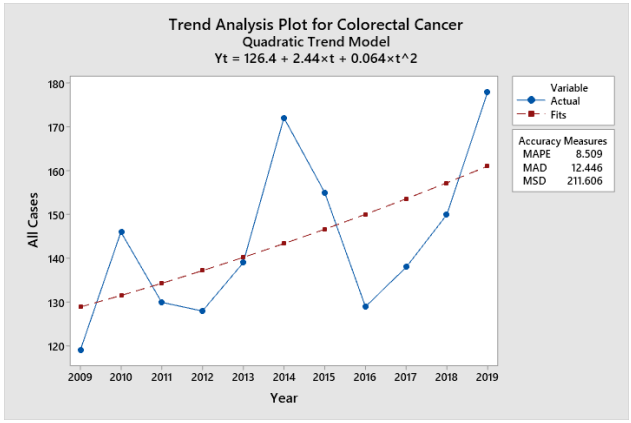
Supplementary File 4.

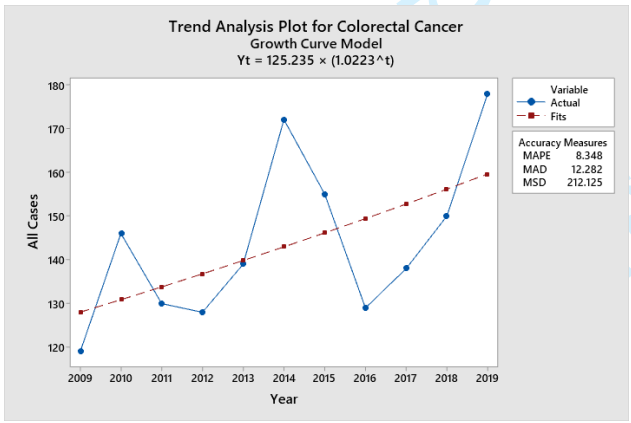
Detailed analysis for forecasting future ten-year incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among all patients based on tumor location and tumor side involvement

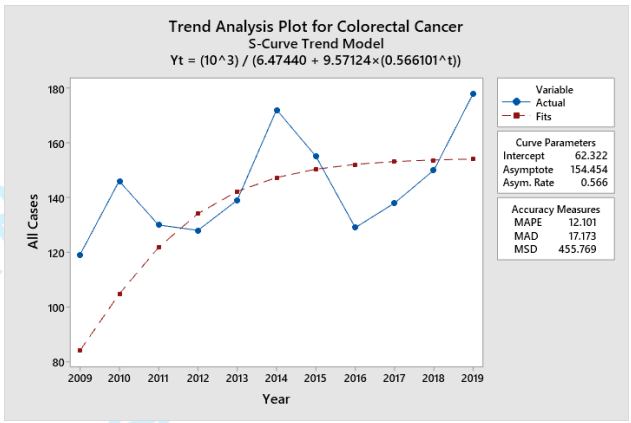
a. Regression Model for Total CRC Cases

1. Curve Options









Model	**Automatic Fitted-Curve**	**Accuracy Measurements**		
		MAPE	**MAD**	**MSD**
Linear	$Yt = 124.7 + 3.21t$	8.518	12.469	211.926
Quadratic	$Yt = 126.4 + 2.44t + 0.064t^2$	8.509	12.446	**211.606**
Exponential Growth*	$\mathbf{Yt = 125.235 \times (1.0223^t)}$	**8.348**	**12.282**	212.125
S-shaped	$Yt = 10^3 / (6.4744 + 9.5712 \times (0.5661^t))$	12.101	17.173	455.769

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.053	1	.053	4.558	.062
Residual	.106	9	.012		
Total	.159	10			

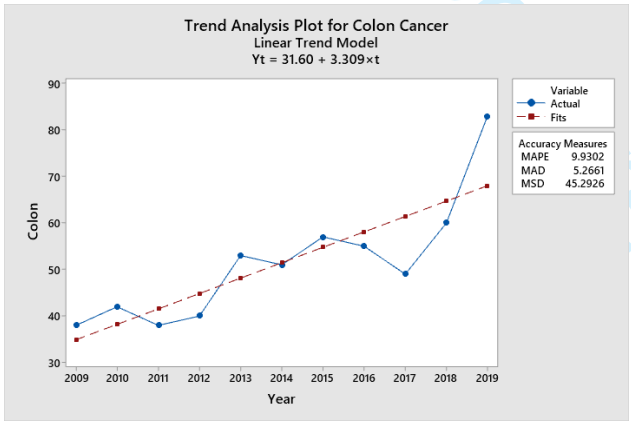
The independent variable is Year.

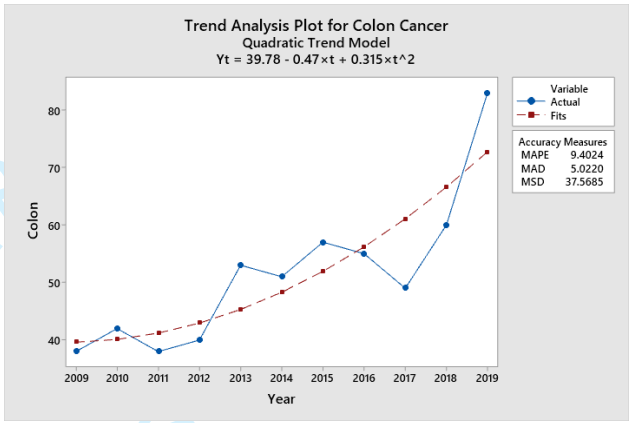
3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

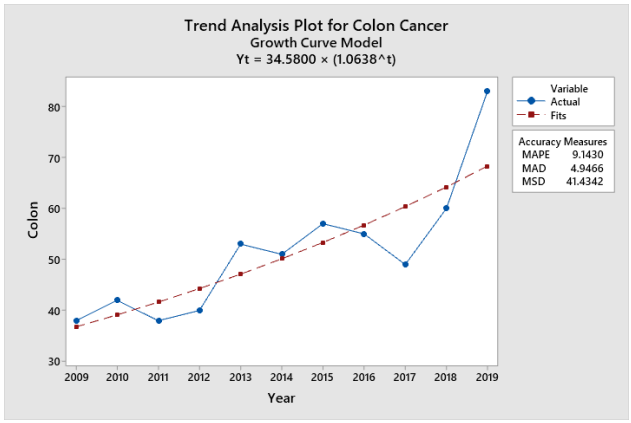
Year	Forecasted Cases
2020	163.163
2021	166.800
2022	170.518
2023	174.319
2024	178.205
2025	182.177
2026	186.238
2027	190.389
2028	194.633
2029	198.972
Mean	**180.541**
Total	**1,805.41**

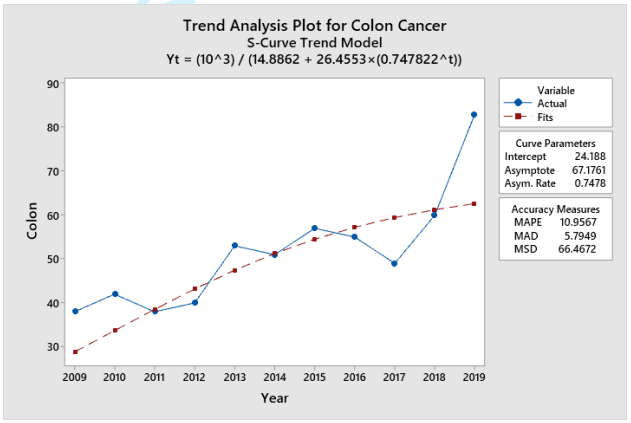
b. Regression Model for Total Colon Cancer Cases

1. Curve Options









Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	**MAD**	**MSD**
Linear	$Yt = 31.60 + 3.309t$	9.9302	5.2661	45.2926
Quadratic	$Yt = 39.78 – 0.47t + 0.315t^2$	9.4024	5.0220	**37.5685**
Exponential Growth*	$\mathbf{Yt = 34.58 \times (1.0638^t)}$	**9.1430**	**4.9466**	41.4342
S-shaped	$Yt = 10^3 / (14.8862 + 26.4553 \times (0.747822^t))$	10.9567	5.7949	66.4672

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.421	1	.421	29.084	**.000**
Residual	.130	9	.014		
Total	.551	10			

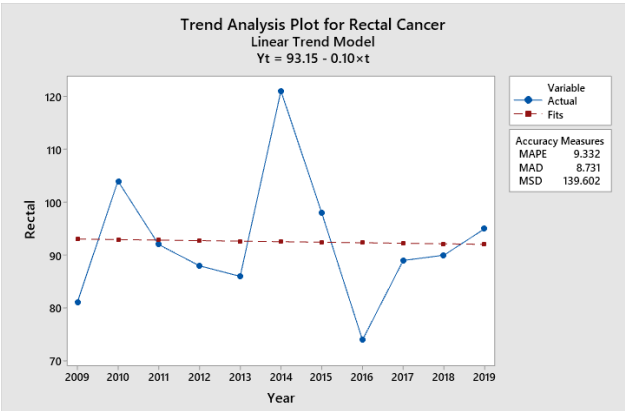
The independent variable is Year.

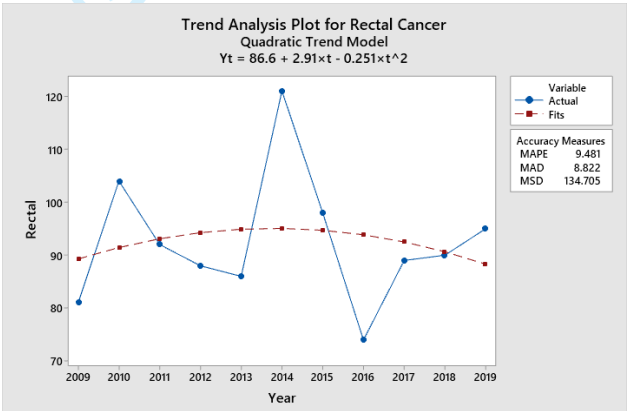
3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

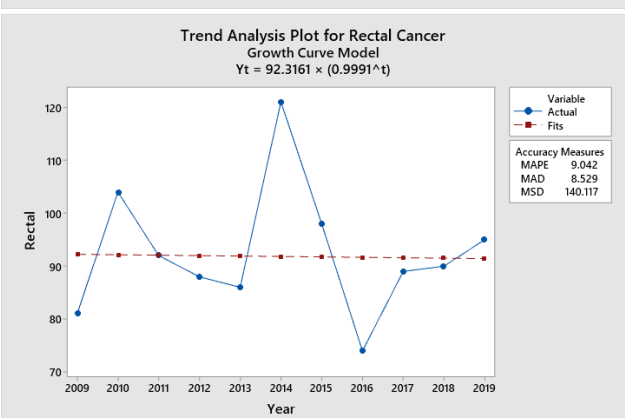
Year	Forecasted Cases
2020	72.652
2021	77.288
2022	82.221
2023	87.468
2024	93.051
2025	98.989
2026	105.307
2027	112.027
2028	119.177
2029	126.783
Mean	**97.4963**
Total	**974.963**

c. Regression Model for Total Rectal Cancer Cases

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 93.15 – 0.10t	9.332	8.731	139.602
Quadratic	Yt = 86.6 + 2.91t + 0.25t^2	9.481	8.822	**134.705**
Exponential Growth*	**Yt = 92.3161 × (0.9991^t)**	**9.042**	**8.529**	140.117
S-shaped	*Error: Can not fit the model to these data*	*n/a*	*n/a*	*n/a*

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.000	1	.000	.005	.948
Residual	.167	9	.019		
Total	.167	10			

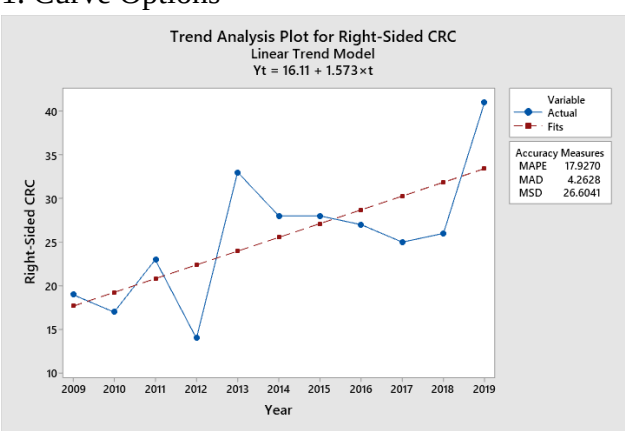
The independent variable is Year.

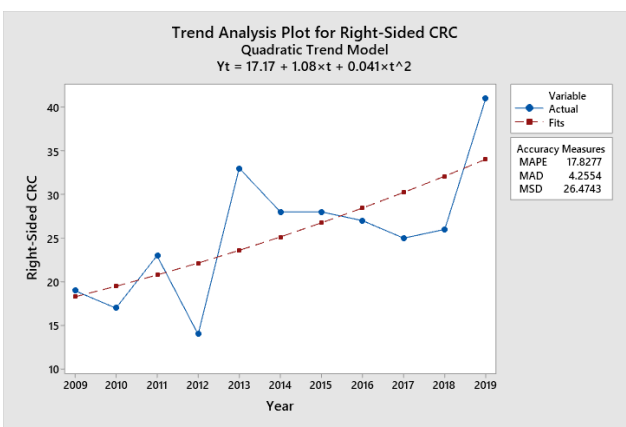
3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

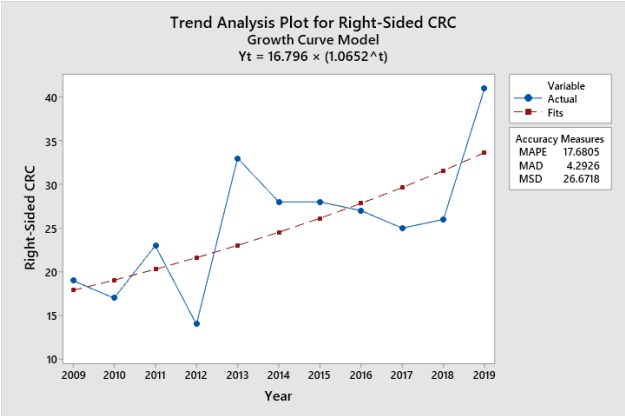
Year	Forecasted Cases
2020	91.3487
2021	91.2685
2022	91.1884
2023	91.1084
2024	91.0284
2025	90.9486
2026	90.8688
2027	90.7890
2028	90.7094
2029	90.6298
Mean	**90.9888**
Total	**909.888**

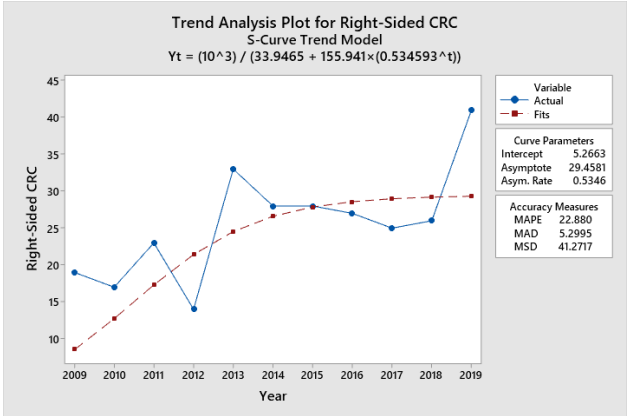
d. Regression Model for Total Right-Sided CRC Cases

1. Curve Options









Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 16.11 + 1.573t$	17.927	4.2628	26.6041
Quadratic*	$\mathbf{Yt = 17.17 + 1.08t + 0.041t^2}$	17.8277	**4.2554**	**26.4743**
Exponential Growth	$Yt = 16.796 \times (1.0652^t)$	**17.6805**	4.2926	26.6718
S-shaped	$Yt = 10^3 / (33.9465 + 155.941 \times (0.534593^t))$	22.8801	5.2995	41.2717

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	272.109	1	272.109	8.369	**.018**
Residual	292.618	9	32.513		
Total	564.727	10			

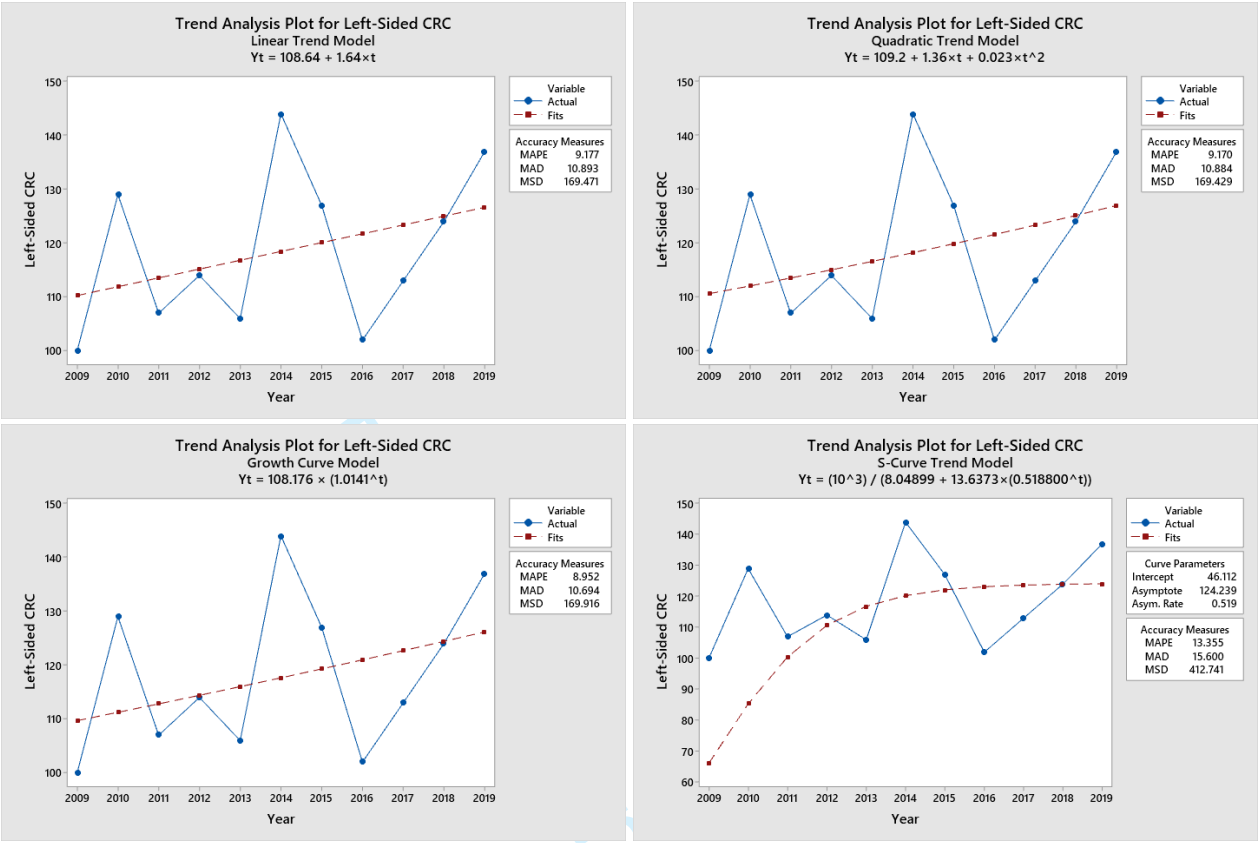
The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

Year	Forecasted Cases
2020	36.0424
2021	38.1455
2022	40.3301
2023	42.5963
2024	44.9441
2025	47.3734
2026	49.8844
2027	52.4769
2028	55.1510
2029	57.9068
Mean	**46.48509**
Total	**464.8509**

e. Regression Model for Total Left-Sided CRC Cases

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 108.64 + 1.64t	9.177	10.893	169.471
Quadratic	Yt = 109.2 + 1.36t + 0.023t^2	9.170	10.884	**169.429**
Exponential Growth*	**Yt = 108.176 × (1.0141^t)**	**8.952**	**10.694**	169.916
S-shaped	Yt = 10^3 / (8.04899 + 13.6373 × (0.518800^t))	13.355	15.600	412.741

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.022	1	.022	1.501	.252
Residual	.129	9	.014		
Total	.150	10			

The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

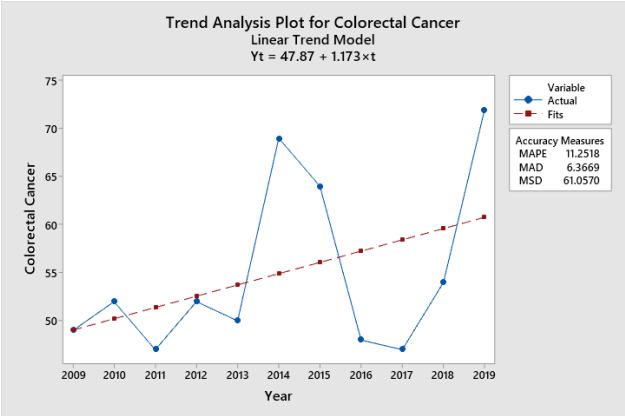
Year	Forecasted Cases
2020	127.936
2021	129.737
2022	131.564
2023	133.416
2024	135.294
2025	137.199
2026	139.131
2027	141.090
2028	143.076
2029	145.090
Mean	**136.3533**
Total	**1363.533**

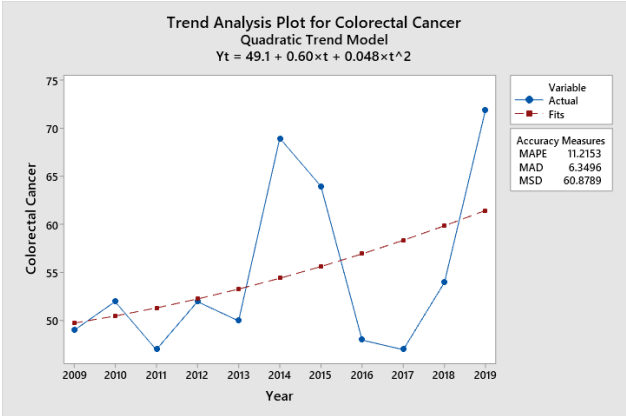
Supplementary File 5.

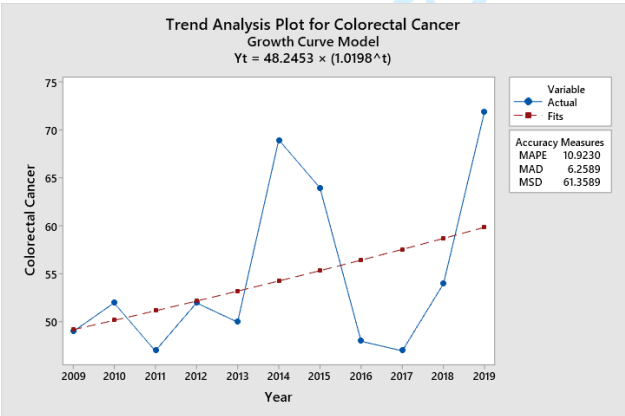
Detailed analysis for forecasting future ten-year incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among young patients based on tumor location and tumor side involvement

a. Regression Model for CRC Cases Among Young Patients

1. Curve Options







Model	**Automatic Fitted-Curve**	**Accuracy Measurements**		
		MAPE	**MAD**	**MSD**
Linear	Yt = 47.87 + 1.173t	11.2518	6.3669	61.0570
Quadratic	Yt = 49.1 + 0.60t + 0.049t^2	11.2153	6.3496	**60.8789**
Exponential Growth*	**Yt = 48.2453 × (1.0198^t)**	**10.9230**	**6.2589**	61.3589
S-shaped	*Error: Can not fit the model to these data*	*n/a*	*n/a*	*n/a*

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.042	1	.042	1.916	.200
Residual	.200	9	.022		
Total	.242	10			

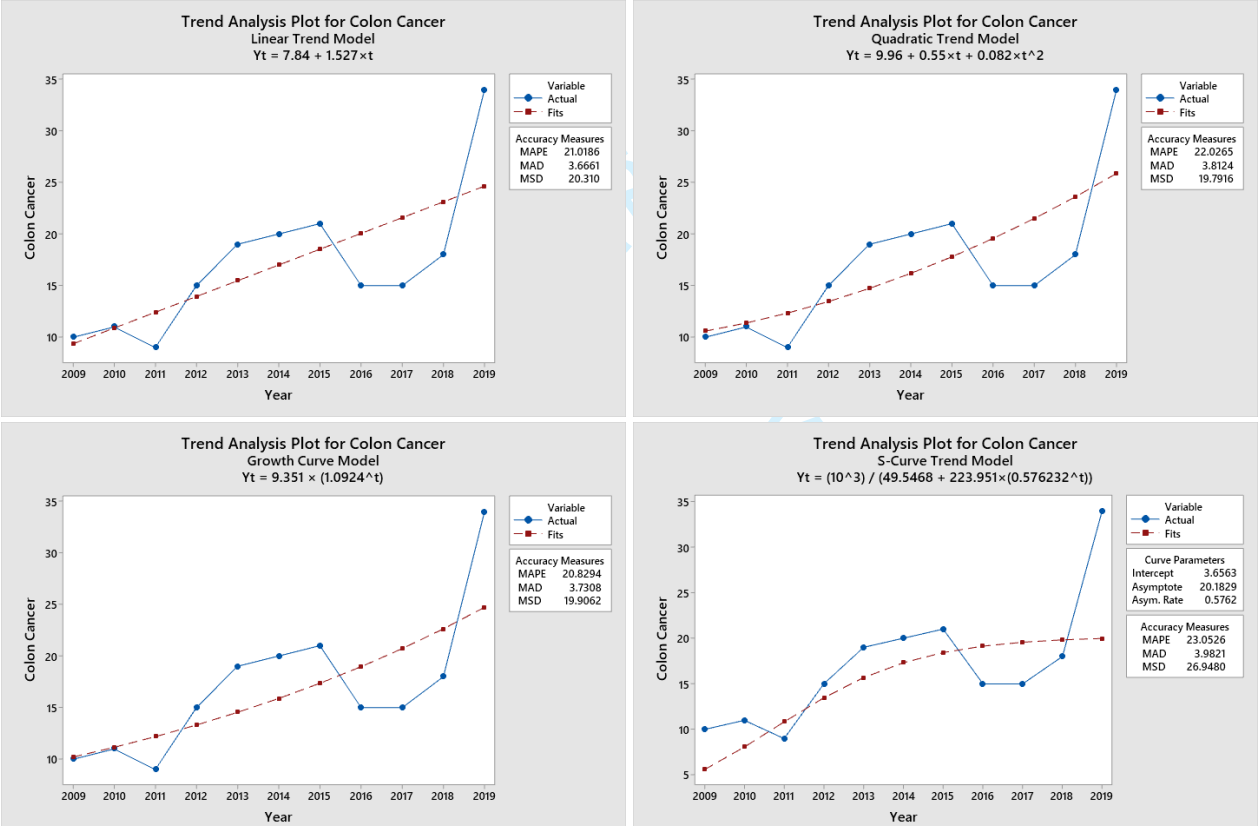
The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

Year	Forecasted Cases
2020	61.0779
2021	62.2902
2022	63.5266
2023	64.7875
2024	66.0734
2025	67.3849
2026	68.7224
2027	70.0864
2028	71.4776
2029	72.8963
Mean	**66.83232**
Total	**668.3232**

b. Regression Model for Colon Cancer Cases Among Young Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	**MAD**	**MSD**
Linear	$Yt = 7.84 + 1.527t$	21.0186	3.6661	20.3107
Quadratic	$Yt = 9.96 + 0.55t + 0.082t^2$	22.0265	3.8124	**19.7916**
Exponential Growth*	**$Yt = 9.351\times (1.0924^t)$**	**20.8294**	**3.7308**	19.9062
S-shaped	$Yt = 10^3 / (49.5468 + (223.951 \times 0.576232^t))$	23.0526	3.9821	26.9480

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.859	1	.859	13.320	**.005**
Residual	.581	9	.065		
Total	1.440	10			

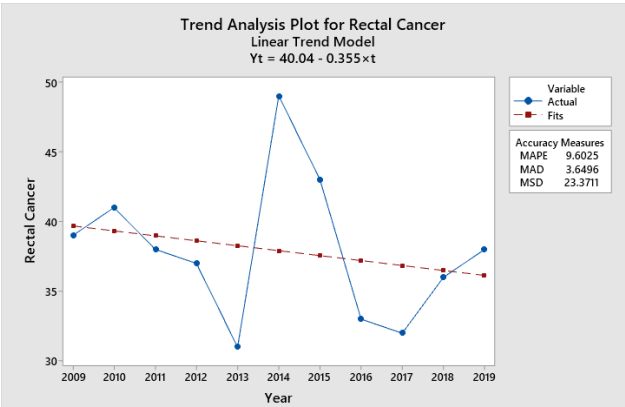
The independent variable is Year.

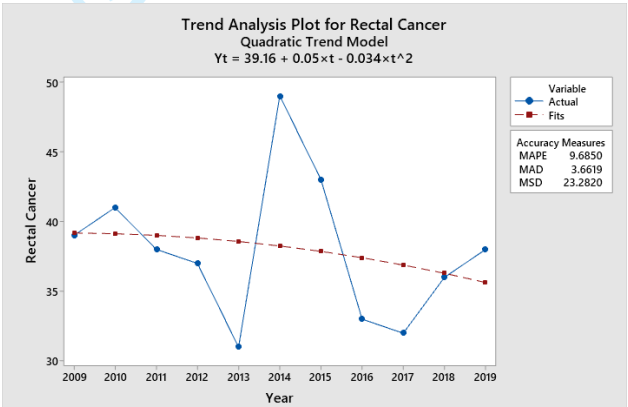
3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

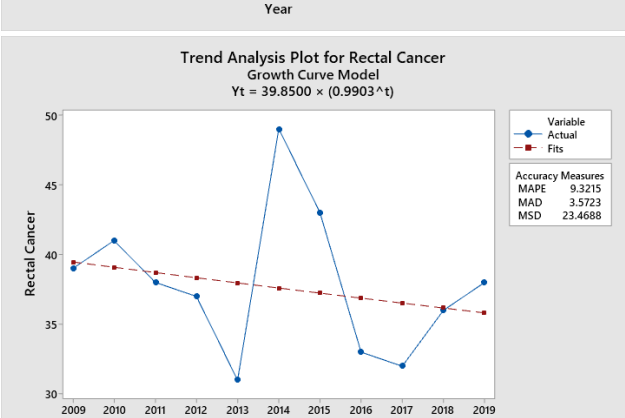
Year	Forecasted Cases
2020	27.0046
2021	29.4998
2022	32.2256
2023	35.2031
2024	38.4559
2025	42.0091
2026	45.8907
2027	50.1310
2028	54.7630
2029	59.8230
Mean	**41.50058**
Total	**415.0058**

c. Regression Model for Rectal Cancer Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 40.04 – 0.355t	9.6025	3.6496	23.3711
Quadratic	Yt = 39.16 + 0.05t – 0.034t^2	9.6850	3.6619	**23.2820**
Exponential Growth*	**Yt = 39.85 × (0.9903^t)**	**9.3215**	**3.5723**	23.4688
S-shaped	*Error: Can not fit the model to these data*	*n/a*	*n/a*	*n/a*

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Exponential growth model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.010	1	.010	.551	.477
Residual	.169	9	.019		
Total	.180	10			

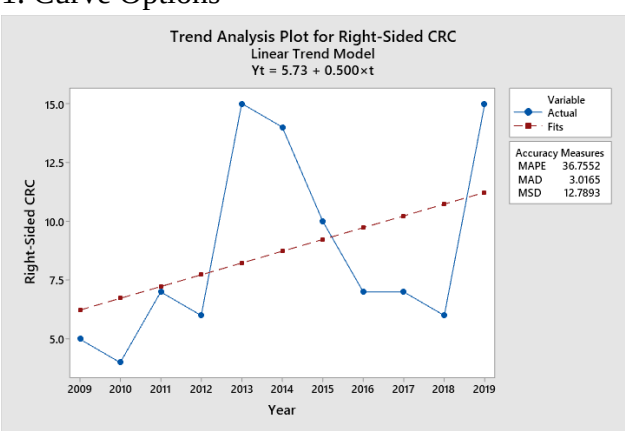
The independent variable is Year.

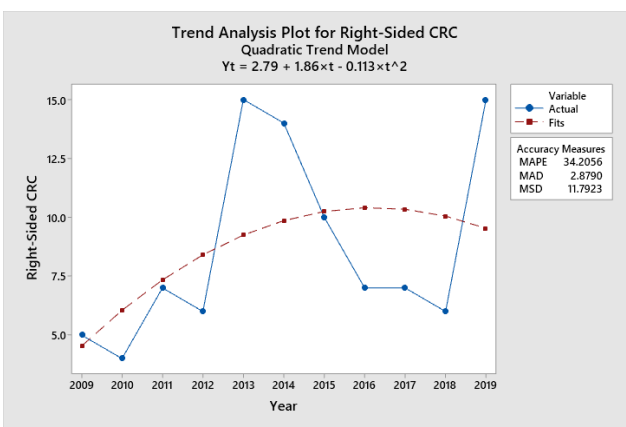
3. The forecast of the number of cases in the following ten-year period using the Exponential growth model.

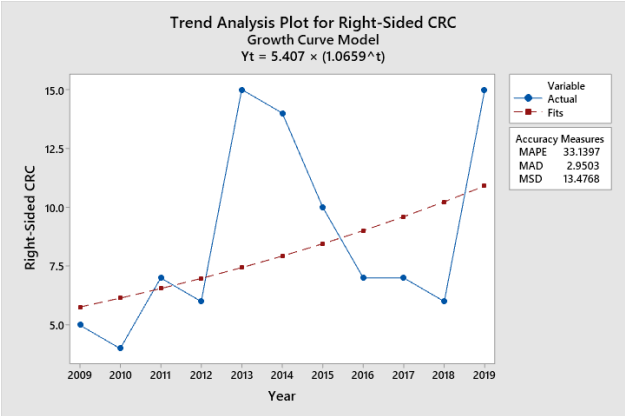
Year	Forecasted Cases
2020	35.4703
2021	35.1278
2022	34.7886
2023	34.4527
2024	34.1201
2025	33.7906
2026	33.4644
2027	33.1413
2028	32.8213
2029	32.5044
Mean	**33.96815**
Total	**339.6815**

d. Regression Model for Right-Sided CRC Cases Among Young Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 5.73 + 0.5t	36.7552	3.0165	12.7893
Quadratic*	**Yt = 2.79 + 1.86t – 0.113t^2**	34.2056	**2.8790**	**11.7923**
Exponential Growth	Yt = 5.407 × (1.0659^t)	**33.1397**	2.9503	13.4768
S-shaped	*Error: Can not fit the model to these data*	*n/a*	*n/a*	*n/a*

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	27.500	1	27.500	1.759	.217
Residual	140.682	9	15.631		
Total	168.182	10			

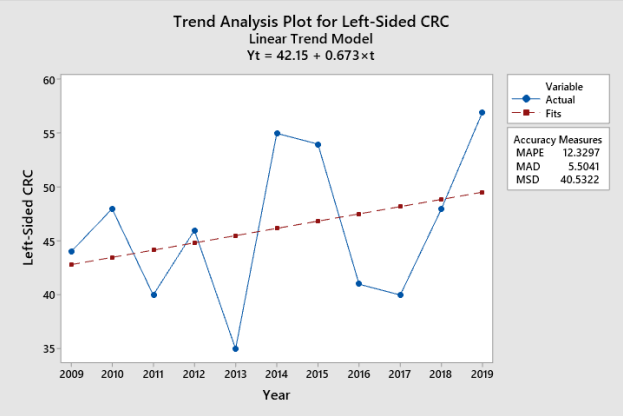
The independent variable is Year.

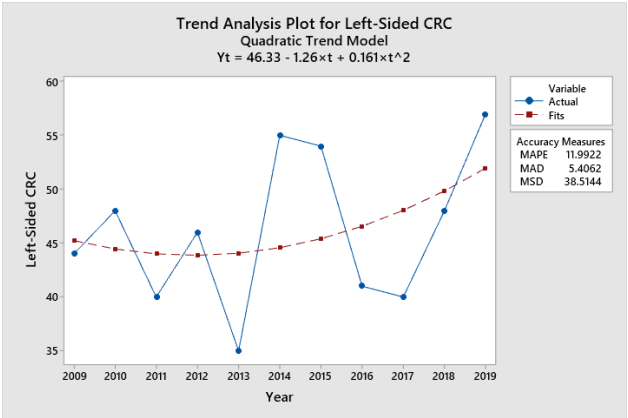
3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

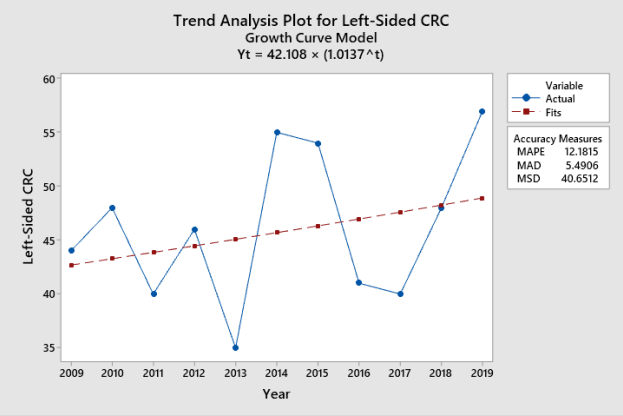
Year	Forecasted Cases
2020	8.78788
2021	7.81818
2022	6.62238
2023	5.20047
2024	3.55245
2025	1.67832
2026	-0.42191
2027	-2.74825
2028	-5.30070
2029	-8.07925
Mean	**1.710957**
Total	**17.10957**

e. Regression Model for Left-Sided CRC Cases Among Young Patients

1. Curve Options







Model	**Automatic Fitted-Curve**	**Accuracy Measurements**		
		MAPE	**MAD**	**MSD**
Linear	Yt = 42.15 + 0.673t	12.3297	5.5041	40.5322
Quadratic*	**$Yt = 46.33 – 1.26t + 0.161t^2$**	**11.9922**	**5.4062**	**38.5144**
Exponential Growth	$Yt = 42.108 \times (1.0137^t)$	12.1815	5.4906	40.6512
S-shaped	*Error: Can not fit the model to these data*	*n/a*	*n/a*	*n/a*

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	49.828	1	49.828	1.006	.342
Residual	445.808	9	49.534		
Total	495.636	10			

The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

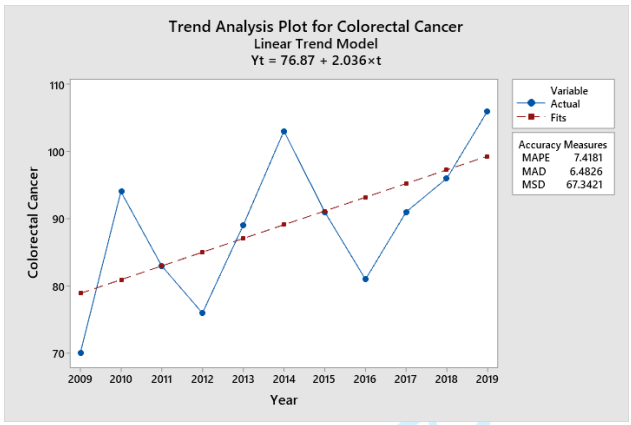
Year	Forecasted Cases
2020	54.4000
2021	57.1636
2022	60.2490
2023	63.6559
2024	67.3846
2025	71.4350
2026	75.8070
2027	80.5007
2028	85.5161
2029	90.8531
Mean	**70.6965**
Total	**706.965**

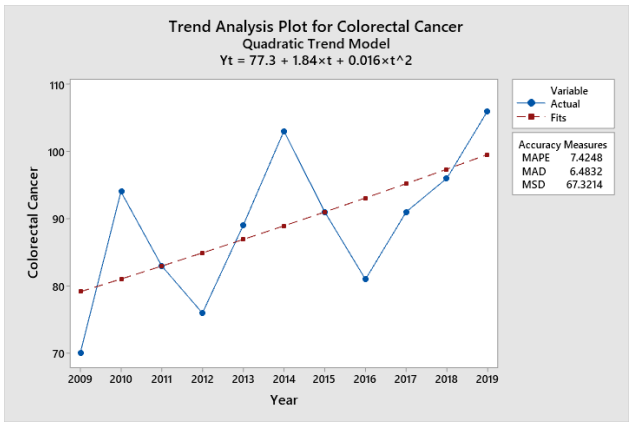
Supplementary File 6.

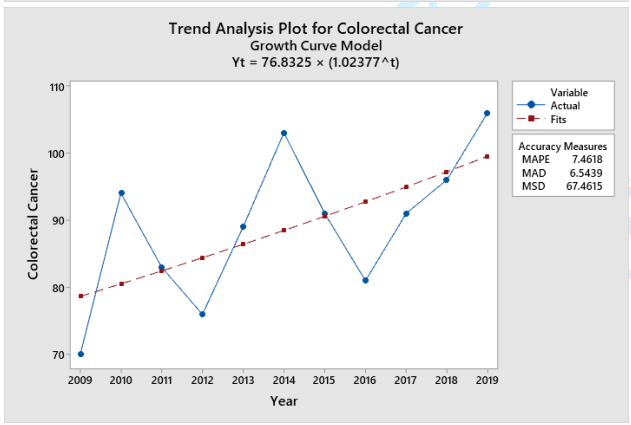
Detailed analysis for forecasting future ten-year incidence of colorectal cancer using the best-fitted curve model obtained from regression analysis among old patients based on tumor location and tumor side involvement

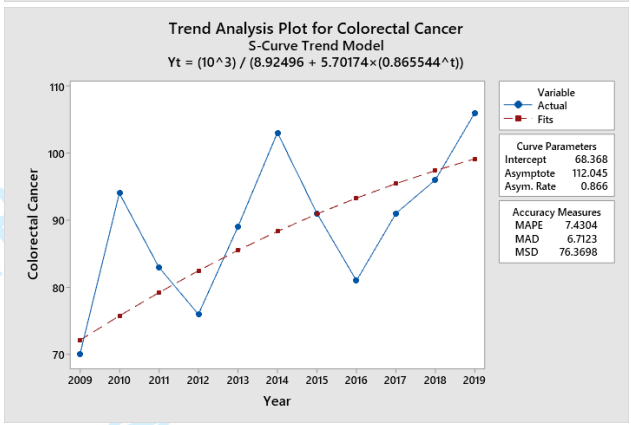
a. Regression Model for CRC Cases Among Old Patients

1. Curve Options









Model	**Automatic Fitted-Curve**	**Accuracy Measurements**		
		MAPE	**MAD**	**MSD**
Linear	Yt = 76.87 + 2.036t	7.4181	**6.4826**	67.3421
Quadratic*	**$Yt = 77.3 + 1.84t + 0.016t^2$**	**7.4248**	6.4832	**67.3214**
Exponential Growth	$Yt = 76.8325 \times (1.02377^t)$	7.4618	6.5439	67.4615
S-shaped	$Yt = 10^3 / (8.92496 + 5.70174 \times (0.865544^t))$	7.4304	6.7123	76.3698

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	456.159	1	456.159	5.542	**.043**
Residual	740.750	9	82.306		
Total	1196.909	10			

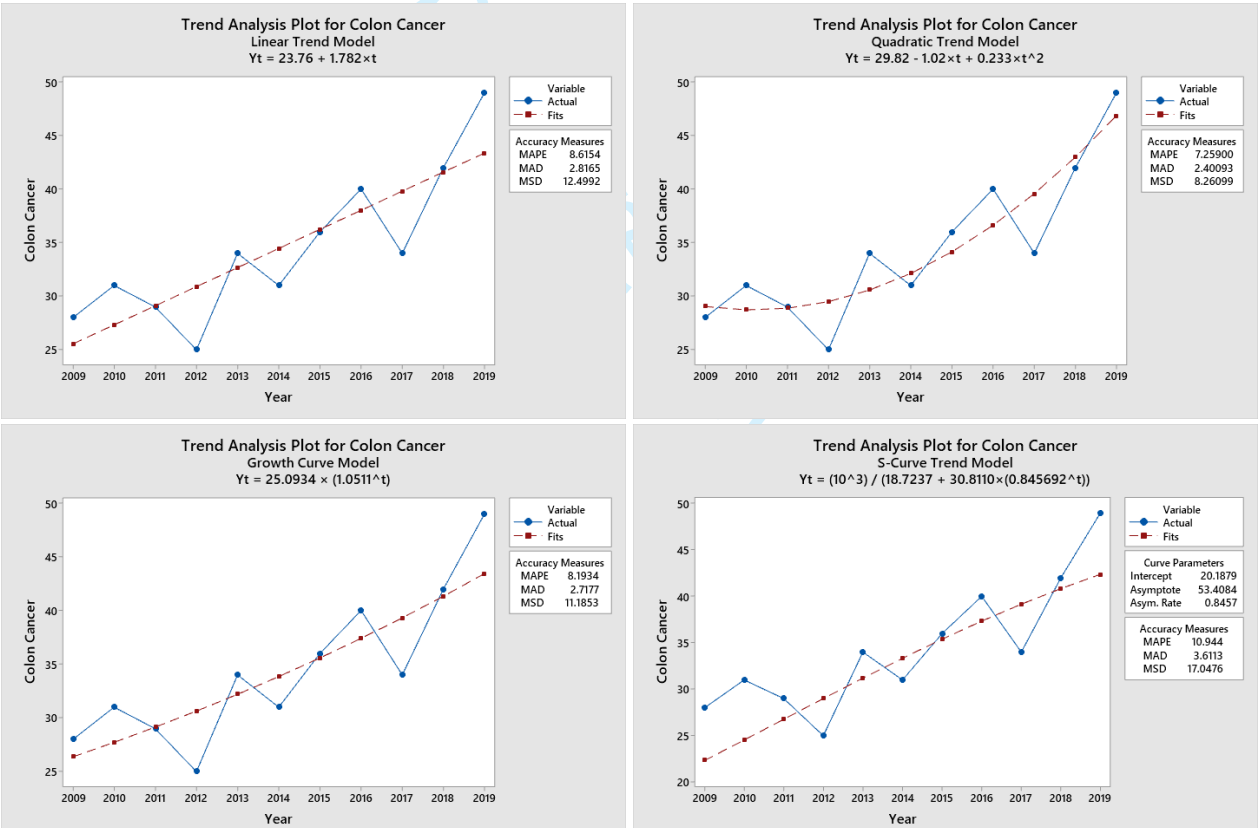
The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

Year	Forecasted Cases
2020	101.733
2021	103.982
2022	106.263
2023	108.577
2024	110.923
2025	113.302
2026	115.714
2027	118.158
2028	120.635
2029	123.145
Mean	**112.2432**
Total	**1122.432**

b. Regression Model for Colon Cancer Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 23.76 + 1.782t$	8.6154	2.8165	12.4992
Quadratic*	$\mathbf{Yt = 29.82 – 1.02t + 0.233t^2}$	**7.2590**	**2.40093**	**8.26099**
Exponential Growth	$Yt = 25.0934 \times (1.0511^t)$	8.1934	2.7177	11.1853
S-shaped	$Yt = 10^3 / (18.7237 + (30.8110 \times 0.845692^t))$	10.9444	3.6113	17.0476

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	349.413	1	349.413	22.902	**.001**
Residual	137.314	9	15.257		
Total	486.727	10			

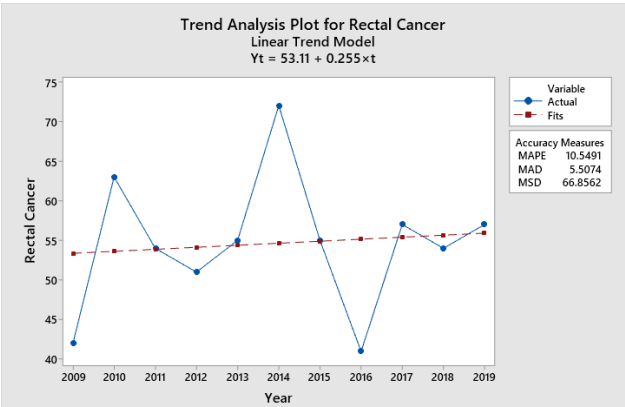
The independent variable is Year.

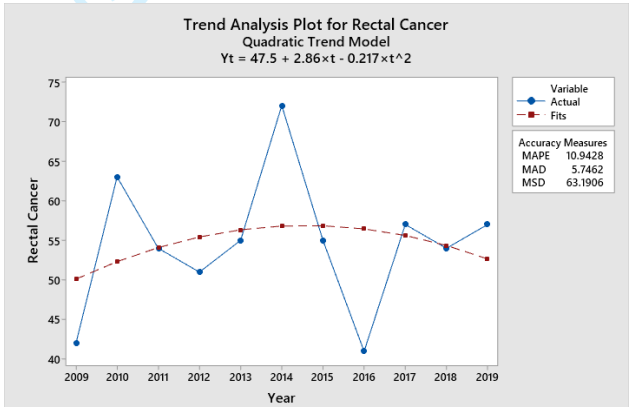
3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

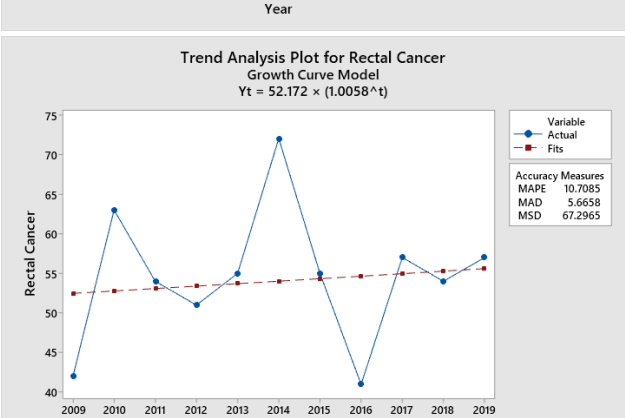
Year	**Forecasted Cases**
2020	51.206
2021	56.018
2022	61.297
2023	67.041
2024	73.252
2025	79.929
2026	87.072
2027	94.681
2028	102.757
2029	111.298
Mean	**78.4551**
Total	**784.551**

c. Regression Model for Rectal Cancer Cases Among Old Patients

1. Curve Options







Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear*	**Yt = 53.11 + 0.255t**	**10.5491**	**5.5074**	66.8562
Quadratic	$Yt = 47.5 + 2.86t - 0.217t^2$	10.9428	5.7462	**63.1906**
Exponential Growth	$Yt = 52.172 \times (1.0958^t)$	10.7085	5.6658	67.2965
S-shaped	Error: Can not fit the model to these data	n/a	n/a	n/a

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Linear model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	7.127	1	7.127	.087	.774
Residual	735.418	9	81.713		
Total	742.545	10			

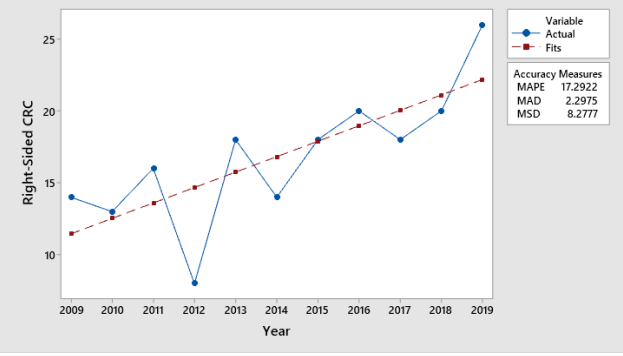
The independent variable is Year.

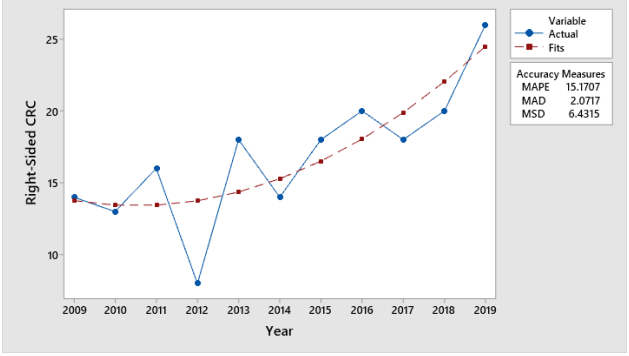
3. The forecast of the number of cases in the following ten-year period using a Linear model.

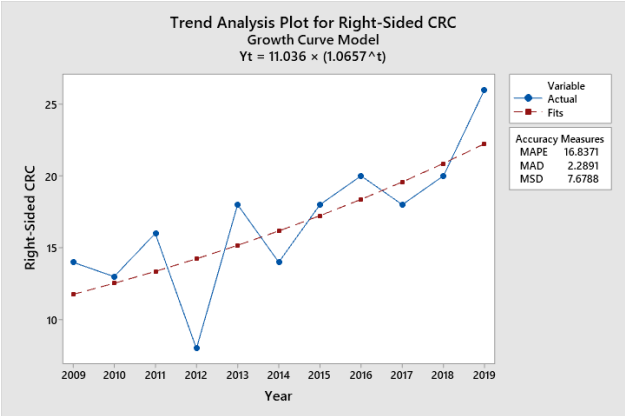
Year	Forecasted Cases
2020	56.1636
2021	56.4182
2022	56.6727
2023	56.9273
2024	57.1818
2025	57.4364
2026	57.6909
2027	57.9455
2028	58.2000
2029	58.4545
Mean	**57.30909**
Total	**573.0909**

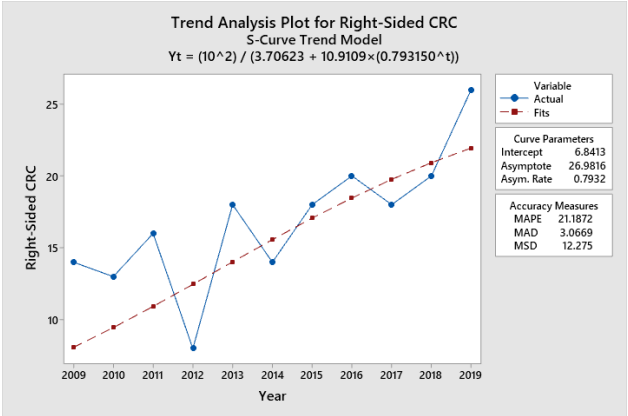
d. Regression Model for Right-Sided CRC Cases Among Old Patients

1. Curve Options









Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	$Yt = 10.38 + 1.073t$	17.2922	2.2975	8.2777
Quadratic*	$\mathbf{Yt = 14.38 - 0.77t + 0.154t^2}$	**15.1707**	**2.0717**	**6.4315**
Exponential Growth	$Yt = 11.036 \times (1.0657^t)$	16.8371	2.2891	7.6788
S-shaped	$Yt = 10^2 / (3.70623 + (10.9109 \times 0.793150^t))$	21.1872	3.0669	12.2758

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., Quadratic model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	126.652	1	126.652	12.528	**.006**
Residual	90.984	9	10.109		
Total	217.636	10			

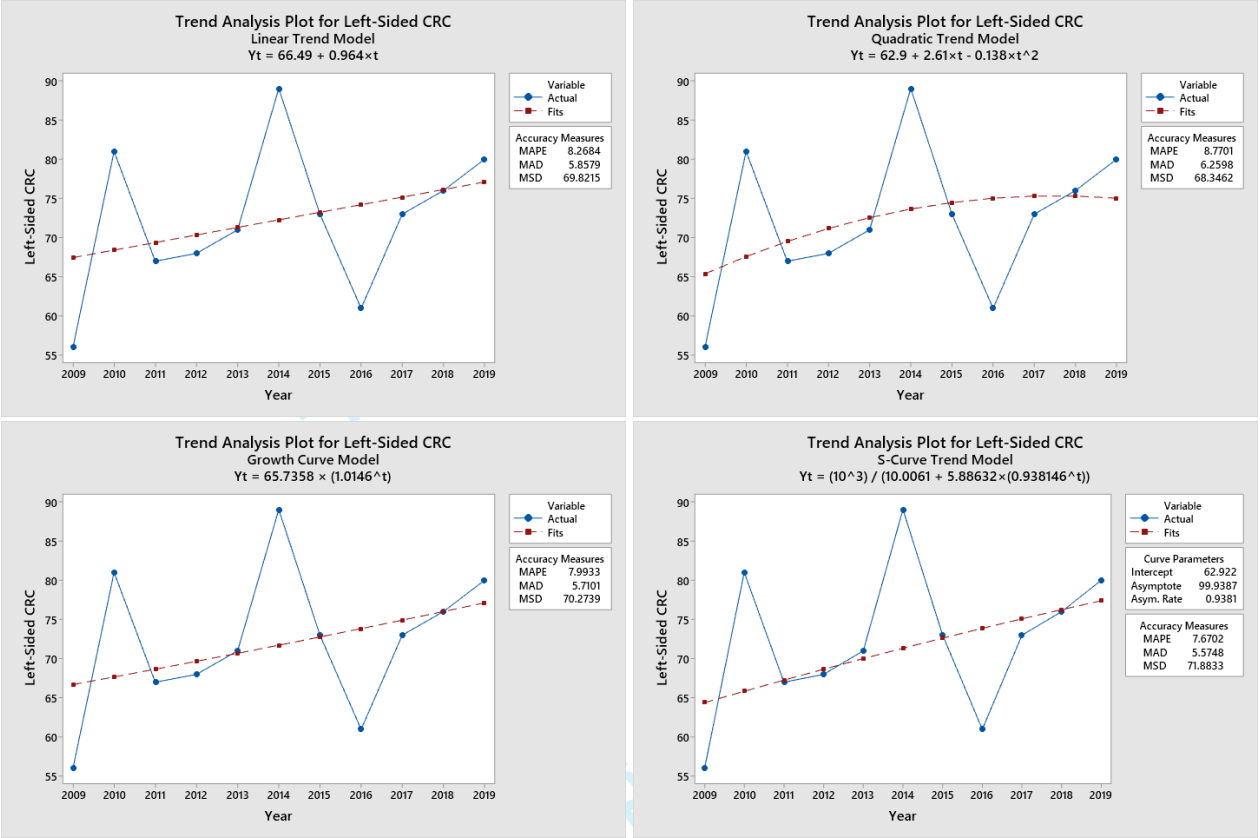
The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using the Quadratic model.

Year	Forecasted Cases
2020	27.2545
2021	30.3273
2022	33.7077
2023	37.3958
2024	41.3916
2025	45.6951
2026	50.3063
2027	55.2252
2028	60.4517
2029	65.9860
Mean	**44.77412**
Total	**447.7412**

e. Regression Model for Left-Sided CRC Cases Among Old Patients

1. Curve Options



Model	Automatic Fitted-Curve	Accuracy Measurements		
		MAPE	MAD	MSD
Linear	Yt = 66.49 + 0964t	8.2684	5.8579	69.8215
Quadratic	$Yt = 62.8 + 2.61t - 0.138t^2$	8.7701	6.2598	**68.3462**
Exponential Growth	$Yt = 65.7358 \times (1.0146^t)$	7.9933	5.7101	70.2739
S-shaped*	**$Yt = 10^3 / (10.0061 + (5.88632 \times 0.938146^t))$**	**7.6702**	**5.5748**	71.8833

**The best-fitted model is the one that has the lowest value for three parameters (MAPE, MAD, and MSD), or at least for two parameters out of three, or at least having the lowest value for MAPE.*

2. The significance test results for the slope of curve estimation (i.e., S-shaped curve model) employing the ANOVA statistical test in SPSS.

ANOVA

	Sum of Squares	df	Mean Square	F	Sig.
Regression	.023	1	.023	1.400	.267
Residual	.149	9	.017		
Total	.172	10			

The independent variable is Year.

3. The forecast of the number of cases in the following ten-year period using an S-shaped curve model.

Year	Forecasted Cases
2020	78.4808
2021	79.5371
2022	80.5543
2023	81.5325
2024	82.4720
2025	83.3733
2026	84.2369
2027	85.0636
2028	85.8540
2029	86.6090
Mean	**82.77135**
Total	**827.7135**

Supplementary Table 1.
The summary of best-fitted models, equations of the predicted case, and several forecasted scenarios between 2020 and 2029.

	Young Patients (<50 years old)					Old Patients (≥50 years old)					All Patients				
	Tumor Locations			Side Involvement		Tumor Locations			Side Involvement		Tumor Locations			Side Involvement	
	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC	CRC	Colon	Rectum	Right-sided CRC	Left-sided CRC
Best-Fitted Model	Exponential Growth	Exponential Growth	Exponential Growth	Quadratic	Quadratic	Quadratic	Quadratic	Linear	Quadratic	S-shaped	Exponential Growth	Exponential Growth	Exponential Growth	Quadratic	Exponential Growth
Predicted Case Equation	$Y_t = 48.2453 \times (1.0198^t)$	$Y_t = 9.351 \times (1.0924^t)$	$Y_t = 39.85 \times (0.9903^t)$	$Y_t = 2.79 + 1.86t - 0.113t^2$	$Y_t = 46.33 - 1.26t + 0.161t^2$	$Y_t = 77.3 + 1.84t + 0.016t^2$	$Y_t = 29.82 - 1.02t + 0.233t^2$	$Y_t = 53.11 + 0.255t$	$Y_t = 14.38 - 0.77t + 0.154t^2$	$Y_t = 10^3 / (10.0061 + (5.88632 \times 0.938146^t))$	$Y_t = 125.6 \times (1.02^t)$	$Y_t = 34.58 \times (1.0638^t)$	$Y_t = 92.3161 \times (0.9991^t)$	$Y_t = 17.17 + 1.08t + 0.041t^2$	$Y_t = 108.176 \times (1.0141^t)$
MAPE	10.9230	20.8294	9.3215	34.2056	11.9922	7.4248	7.2590	10.5491	15.1707	7.6702	8.3457	9.1430	9.042	17.8277	8.952
MAD	6.2589	3.7308	3.5723	2.8790	5.4062	6.4832	2.40093	5.5074	2.0717	5.5748	12.2617	4.9466	8.529	4.2554	10.694
MSD	61.3589	19.9062	23.4688	11.7923	38.5144	67.3214	8.26099	66.8562	6.4315	71.8833	217.1	41.4342	140.117	26.4743	169.916
p-value of slope	0.200	0.005	0.477	0.217	0.342	0.043	0.001	0.774	0.006	0.267	0.005	<0.001	0.948	0.018	0.252
2020	61.08	27.00	35.47	8.79	54.40	101.73	51.21	56.16	27.25	78.48	166.16	72.65	91.35	36.04	127.94
2021	62.29	29.50	35.13	7.82	57.16	103.98	56.02	56.42	30.33	79.54	166.80	77.29	91.27	38.15	129.74
2022	63.53	32.23	34.79	6.62	60.25	106.26	61.30	56.67	33.71	80.55	169.52	82.22	91.19	40.33	131.56
2023	64.79	35.20	34.45	5.20	63.66	108.58	67.04	56.93	37.40	81.53	173.32	87.47	91.11	42.60	133.42
2024	66.07	38.46	34.12	3.55	67.38	110.92	73.25	57.18	41.39	82.47	178.21	93.05	91.03	44.94	135.29
2025	67.38	42.01	33.79	1.68	71.44	113.30	79.93	57.44	45.70	83.37	184.18	98.99	90.95	47.37	137.20
2026	68.72	45.89	33.46	-0.42	75.81	115.71	87.07	57.69	50.31	84.24	191.24	105.31	90.87	49.88	139.13
2027	70.09	50.13	33.14	-2.75	80.50	118.16	94.68	57.95	55.23	85.06	199.39	112.03	90.79	52.48	141.09
2028	71.48	54.76	32.82	-5.30	85.52	120.64	102.76	58.20	60.45	85.85	208.63	119.18	90.71	55.15	143.08
2029	72.90	59.82	32.50	-8.08	90.85	123.15	111.30	58.45	65.99	86.61	218.97	126.78	90.63	57.91	145.09
Total ten years	66.83	41.50	33.97	1.71	70.70	112.24	78.46	57.31	44.77	82.77	190.54	97.50	90.99	46.49	136.35
Mean per year	668.32	415.01	339.68	17.11	706.97	1122.43	784.55	573.09	447.74	827.71	1885.41	974.96	909.89	464.85	1363.53

Notes:

- Y_t is the variable (equation for predicted cases), and t is the time unit (year) value.
- The best-fitted model and the most precise predicted case equation were decided from the one model that had the lowest accuracy value for the three measured parameters (i.e., MAPE, MAD, and MSD) or at least having two lowest parameters out of the three, or at least having the lowest value for MAPE if the two former conditions were not met.
- P-value was obtained from the ANOVA test for curve estimation

Abbreviation:
CRC, colorectal cancer; MAPE, mean absolute percent error; MAD, mean absolute deviation; MSD, mean square deviation.

Research Checklist
STROBE Checklist 2007 (v4) Statement For Reporting A Cross-Sectional Study

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2
Objectives	3	State specific objectives, including any prespecified hypotheses	2
Methods			
Study design	4	Present key elements of study design early in the paper	2-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	2-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	2-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	3
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	2-3
Bias	9	Describe any efforts to address potential sources of bias	16-17
Study size	10	Explain how the study size was arrived at	2-3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	3
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	4
		(*b*) Describe any methods used to examine subgroups and interactions	4
		(*c*) Explain how missing data were addressed	4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	4
		(*e*) Describe any sensitivity analyses	4
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	4-5
		(b) Give reasons for non-participation at each stage	3, 4-5
		(c) Consider use of a flow diagram	3
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	4-8
		(b) Indicate number of participants with missing data for each variable of interest	3, 4
Outcome data	15*	Report numbers of outcome events or summary measures	4-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	4-8
		(*b*) Report category boundaries when continuous variables were categorized	4-8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a	N/A

		meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	4-8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	1-2, 12, and 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.