

Original Article

National Data on Colorectal Cancer Trends: A Population-Based Study in Taiwan

Chia-Lin Chou^{1,2}
Shih-Feng Weng^{3,4}
Li-Chin Cheng¹
Yu-Feng Tian¹

¹Division of General Surgery, Department of Surgery, Chi-Mei Medical Center, Tainan,

²Division of Colon & Rectal Surgery, Department of Surgery, Taipei Veterans General Hospital and National Yang-Ming University, Taipei,

³Department of Medical Research, Chi Mei Medical Center,

⁴Department of Hospital and Health Care Administration, Recreation and Health-Care Management, Chia-Nan University of Pharmacy and Science, Tainan, Taiwan

Key Words

Colorectal cancer;
Age;
Prognosis

Abbreviations

CRC, colorectal cancer;
NHI, National Health Insurance

Purpose. The prognosis of patients having different ages at the onset of colorectal cancer (CRC) is controversial. The aim of this study was to complete a comprehensive analysis of the relationship between age differences and CRC survival using population registries from Taiwan.

Methods. For patients diagnosed with CRC between 1998 and 2005, we analyzed survival data derived from the Taiwan Cancer Registry database. During this time period, 65,113 patients were registered, and 62,060 patients, presenting definite histological evidence of adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma of the colon and rectum, were enrolled into this cohort study. Age differences in pathological characteristics and prognosis were analyzed.

Results. From 1998 to 2005, the proportion of patients diagnosed at a younger age (≤ 40 -years-of-age group) decreased from 6.8% to 4.6%. Until 2000, most individuals in the CRC patient group were in the sixth and seventh decade. Individuals in the seventh and eighth decade replaced this group after 2000, and became the majority. Younger patients (≤ 40 -years-of-age group) had a higher incidence of mucinous adenocarcinoma ($p < 0.001$) and signet-ring cell carcinoma ($p < 0.001$), and poorer 1-year, 3-year, 5-year overall survival ($p < 0.001$) and cancer-specific survival ($p < 0.001$) than elderly patients (the 41-50, 51-60, and 61-70 year groups).

Conclusions. National data on colorectal cancer trends clearly indicate that currently, in Taiwan, colorectal cancer rates are not showing an increase in younger generations. More aggressive histopathologic characteristics and poorer overall and cancer-specific survival were noted in younger, as compared to older CRC patients.

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Annually, almost one million people are diagnosed with colorectal cancer and half a million die from this disease worldwide.¹ CRC is currently the most common cancer in Taiwan. Despite screening, diagnosis, and treatment advances, as well as significant progress in chemotherapeutic approaches, CRC remains the third most common cause of cancer-related death in Taiwan.² A number of factors have been established to

influence survival in patients with CRC, and these include age at onset, gender, stage, mode of presentation, nature of surgery, and pathologic features. The features and prognosis of CRC in younger patients are still controversial and not conclusive. Certain studies revealed a more advanced stage of disease at the time of diagnosis,³⁻⁷ more aggressive histopathological characteristics,⁸⁻¹³ and poorer prognosis in younger as compared to

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Correspondence to: Dr. Yu-Feng Tian, Division of General Surgery, Department of Surgery, Chi-Mei Medical Center, No. 901, Zhonghua Road, Yongkang Dist., Tainan City 710, Taiwan. Tel: +886-6-281-2811; Fax: +886-6-281-4813; E-mail: cmh7590@mail.chimei.org.tw

older patients.¹⁴⁻¹⁷ However, other studies contradict these findings.¹⁸⁻²³ The aim of the present cohort study was to determine whether age differences represent a prognostic factor in CRC.

Methods

Data acquisition and study population

The Taiwan Cancer Registry, a population-based cancer registry, was established in 1979 and covers all of Taiwan. Hospitals with 50 or more beds, providing outpatient and inpatient cancer care, were recruited to participate by reporting all newly diagnosed malignant neoplasms to the registry. The study cohort consisted of all individuals with colon and rectal cancer (ICD-9 153.0, 153.1, 153.2, 153.3, 153.4, 153.5, 153.6, 153.7, 153.8, 153.9, 154.0, 154.1, 154.2, 154.3, and 154.8) reported to the Taiwan Cancer Registry from 1998 through 2005. The following pieces of information were selected from the registry: date of birth; date of diagnosis; age; gender; diagnostic methods; cancer sites; histology; grade of differentiation; date of death; and ICD-9 reporting the cause of death. Information on the date and cause of death was checked with data received by the cancer registration system through linkage with the Registrar General. Deaths up to the end of 2008 were included in the analysis. Patients were included only if the histology codes were consistent with adenocarcinoma, mucinous adenocarcinoma, or signet-ring cell carcinoma of the colon and rectum. Patients were excluded if their histology codes were consistent with squamous-cell carcinoma ($n = 317$), gastrointestinal stromal sarcoma ($n = 103$), carcinoid tumor ($n = 347$), malignant melanoma ($n = 69$), sarcoma ($n = 124$), lymphoma ($n = 244$), or another, not otherwise specified malignancy ($n = 101$; Fig. 1). Tumors occurring from the cecum to the sigmoid colon were included in the colon group, while tumors of the recto-sigmoid junction and rectum were classified into the rectal group.

Statistical analysis

All data were recorded using a standard data form

and analyzed using SPSS 16.0 (SPSS, Inc., Chicago, IL, USA). Quantitative values were compared using a t-test for independent groups. For categorical data, the chi-square or Fisher's exact test were applied. Survival was calculated in months from the date of diagnosis to the date of death. Survival curves were constructed using the Kaplan-Meier method and survival differences were compared with the log-rank test. The level of statistical significance was set at $p < 0.001$. All reported p values are two-tailed.

Results

Patients and clinical data

Based on the Taiwan Cancer registry database, 62,060 patients with CRC diagnosed between 1998 and 2005 were enrolled into this study (Fig. 1). Analyzing the distribution of colorectal cancer by different age groups revealed that there were around 400 newly diagnosed CRC cases in the ≤ 40 -years-of-age group. During the same period, a decrease from 6.8% to 4.6% in the proportion of patients diagnosed at a younger age (≤ 40 -years-of-age group) was noted. Until 2000, patients in the sixth and seventh decade comprised the majority of the CRC group. Subsequently, patients in the seventh and eighth decade re-

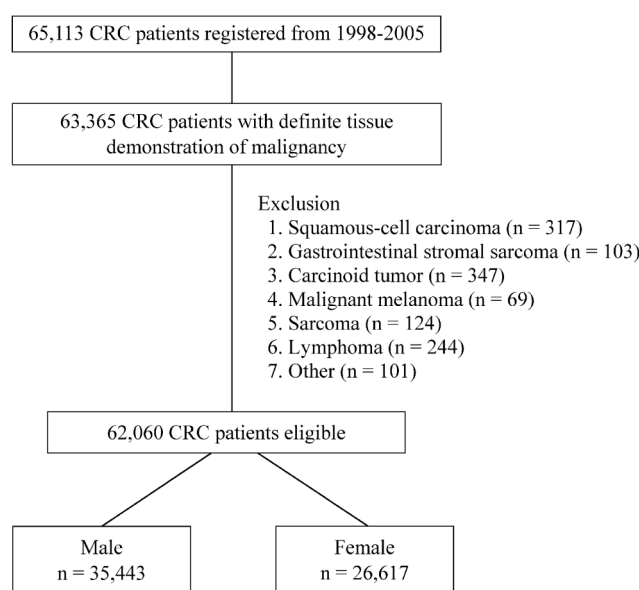


Fig. 1. Diagram of the study flow.

placed them and became the majority (Table 1). Patients' characteristics are shown in Table 2. The mean patient age was 64.9 ± 13.6 years. Women ($n = 26,617$ [42.9%]) were significantly younger (mean age, 64.3 ± 14.2 years) than men ($n = 35,443$ [57.1%]; mean age, 65.3 ± 13.2 years; $p < 0.001$) at the time of CRC diagnosis. There were no differences in the histologic distribution of the cancer types between men and women. Among women diagnosed with CRC, 65.4% had colon cancer, which is a higher percentage than that of the CRC-diagnosed men who had colon cancer (62.4%). There were 33,702 deaths (19,965 men and 13,737 women) and 28,362 cancer-related deaths (16,620 men and 11,742 women). There was a statistically significant difference in histology type, and the 1-year, 3-year, 5-year overall and cancer-specific survival between different age groups with CRC ($p < 0.001$). Mucinous adenocarcinoma and signet-ring cell carcinoma represented 7.71% and 2.43% of the

cancers in younger CRC patients (≤ 40 -years-of-age group). The younger patients (≤ 40 -years-of-age group) had 1-, 3-, 5-year overall survival rates of 82.38%, 60.37%, 53.83% and 83.05%, 61.54%, and 55.14% cancer-specific survival rates, respectively (Table 3). Younger patients (≤ 40 -years-of-age group) had a higher incidence of mucinous adenocarcinoma ($p < 0.001$), signet-ring cell carcinoma ($p < 0.001$), and poorer 1-year, 3-year, 5-year overall survival ($p < 0.001$) and cancer-specific survival ($p < 0.001$) than elderly patients (41-50, 51-60, and 61-70 year groups, shown in Table 3).

Discussion

CRC is perceived as a disease of older persons, but as many as 7% of the patients who develop CRC are under 40 years of age at the time of diagnosis.^{3,24}

Table 1. Distribution of colorectal cancer by age, Taiwan, 1998-2005*

	1998	1999	2000	2001	2002	2003	2004	2005
≤ 40 years	415 (6.8%)	419 (6.4%)	417 (5.9%)	384 (5.4%)	448 (5.6%)	416 (5.1%)	481 (5.0%)	442 (4.6%)
41-50 years	700 (11.5%)	714 (11.0%)	808 (11.4%)	832 (11.7%)	851 (10.6%)	896 (11.0%)	983 (10.3%)	950 (9.9%)
51-60 years	1057 (17.3%)	1104 (16.9%)	1167 (16.5%)	1085 (15.2%)	1262 (15.8%)	1328 (16.3%)	1668 (17.5%)	1679 (17.5%)
61-70 years	1861 (30.5%)	1925 (29.5%)	2080 (29.5%)	2035 (28.6%)	2082 (26.1%)	2154 (26.5%)	2528 (26.5%)	2557 (26.7%)
71-80 years	1618 (26.5%)	1793 (27.5%)	1921 (27.2%)	2078 (29.2%)	2503 (31.3%)	2414 (29.7%)	2777 (29.1%)	2733 (28.5%)
> 80 years	456 (7.5%)	560 (8.6%)	667 (9.4%)	711 (10.0%)	846 (10.6%)	927 (11.4%)	1110 (11.6%)	1218 (12.7%)
Total	6107	6515	7060	7125	7992	8135	9547	9579

* Data are given as number of patients and obtained from the Taiwan Cancer Registry Data Base.

Table 2. Demographic characteristics of 62,060 CRC patients by gender, 1998-2005

	Men (n = 35,443)	Women (n = 26,617)	p value
Mean age (years)	65.3 ± 13.2	64.3 ± 14.2	< 0.001
Age at diagnosis (years)			< 0.001
≤ 40	1761 (5.0%)	1661 (6.2%)	
41-50	3437 (9.7%)	3297 (12.4%)	
51-60	5852 (16.5%)	4498 (16.9%)	
61-70	10123 (28.6%)	7099 (26.7%)	
71-80	10840 (30.6%)	6997 (26.3%)	
> 80	3430 (9.7%)	3065 (11.5%)	
Histology			0.005
Adenocarcinoma	33907 (95.7%)	25371 (95.3%)	
Mucinous adenocarcinoma	1336 (3.8%)	1122 (4.2%)	
Signet-ring cell carcinoma	200 (0.6%)	124 (0.5%)	
Site			< 0.001
Colon	22100 (62.4%)	17413 (65.4%)	
Rectum	13343 (37.6%)	9204 (34.6%)	

Table 3. Pathological characteristics, overall survival, and cancer-specific survival in different age groups

Age at diagnosis (years)	≤ 40 years (N = 3422)	41-50 years (N = 6734)	51-60 years (N = 10350)	61-70 years (N = 17222)	71-80 years (N = 17837)	> 80 years (N = 6495)	<i>p</i> value
Histology							< 0.0001**
Adenocarcinoma	3075 (89.86%)	6306 (93.64%)	16562 (96.17%)	9895 (95.60%)	17163 (96.22%)	6277 (96.64%)	
Mucinous adenocarcinoma	264 (7.71%)	366 (5.44%)	416 (4.02%)	604 (3.51%)	604 (3.369%)	204 (3.14%)	
Signet-ring cell carcinoma	83 (2.43%)	62 (0.92%)	39 (0.38%)	56 (0.33%)	70 (0.39)	14 (0.22%)	
1-years survival	82.38%	85.79%	86.98%	83.46%	75.39%	59.94%	< 0.0001***
1-years Cancer-specific survival	83.05%	86.62%	88.05%	85.23%	78.43%	65.96%	< 0.0001***
3-years survival	60.37%	66.31%	68.72%	64.50%	54.84%	36.44%	< 0.0001***
3-years Cancer-specific survival	61.54%	68.13%	71.17%	68.43%	61.24%	48.18%	< 0.0001***
5-years survival	53.83%	58.72%	60.79%	55.97%	45.30%	27.24%	< 0.0001***
5-years Cancer-specific survival	55.14%	61.02%	64.16%	61.50%	54.27%	42.54%	< 0.0001***

* Data are given as number of patients and obtained from the Taiwan Cancer Registry Data Base; ** Obtained by chi-square;

*** obtained by log rank test.

In this Taiwanese population-based study, between 1998 and 2005 there were around 400 newly diagnosed CRC cases in the ≤ 40-years-of-age group. During the same periods, the number of patients with newly diagnosed CRC increased from 6000 to 9500 annually, resulting in a decrease, from 6.8% to 4.6%, in the proportion of patients diagnosed at a younger age (≤ 40-years-of-age group). Until 2000, individuals in the sixth and seventh decade comprised the majority of the CRC patients, but after that, individuals in the seventh and eighth decades replaced this group and became the majority. To clear definition of colorectal trends in Taiwan, we calculated age-specific colorectal cancer incidence rate for each generations during these periods (Table 4). In the younger age group (≤ 40-years-of-age), the colorectal cancer incidence rate increased slightly from 2.81 per 100,000 person-years to 3.22 per 100,000 person-years ($p = 0.034$). The incidence of colorectal cancers among the nation's younger generation is not on an obvious rise. However, the colorectal incidence rate increased dramatically in the elderly group (71-80 and > 80 year group, $p = 0.001$ and $p < 0.001$). National data on colorectal cancer trends clearly reveal that no increased colorectal cancer rates exist, at present, in younger generations in Taiwan. Colorectal cancer in Taiwan is indeed a disease of the elderly patients.

Due to the typically slow development of CRC,

there is a large potential for reducing the disease burden by early detection and by removing lesions that are precancerous or in the early stages of malignancy. Various screening approaches, including fecal occult blood testing (FOBT), sigmoidoscopy, and colonoscopy, have in the meanwhile been recommended by expert committees and implemented in screening programs offered in a number of countries.²⁵⁻²⁸ The use of either annual or biennial fecal occult-blood testing significantly reduces the incidence of colorectal cancer.²⁹ Regarding the recommended age for initiating screening, which is a crucial parameter for the effectiveness and cost-effectiveness of screening programs, some variation exists between countries, typically ranging from 50 to 60 years in average-risk populations. In Taiwan, since 2004, the Bureau of Health Promotion proposed biennial fecal occult-blood testing in people 50 to 69 years old. According to the current study, individuals in the seventh and eighth decades became the majority of CRC cases since 2001, but the current biennial fecal occult-blood testing program did not cover the eighth decade population, the major group of CRC. Expanding the inclusion criteria to the eighth decade for biennial fecal occult-blood testing seems to be worth considering.

Most previous studies did not find significant differences in the gender distribution among CRC patients, regardless of age. In our study, we found that

Table 4. Age-specific colorectal cancer incidence rate, Taiwan, 1998-2005*

	1998 (rate [#])	1999	2000	2001	2002	2003	2004	2005	linear trend	
									Estimate	<i>p</i> value
≤ 40 years										
Case number	415 (2.81)	419 (2.86)	417 (2.86)	384 (2.66)	448 (3.13)	416 (2.95)	481 (3.45)	442 (3.22)	0.078	0.034
Total population	14743708	14651011	14570903	14438778	14291528	14112812	13928336	13747992		
41-50 years										
Case number	700 (22.43)	714 (21.93)	808 (23.96)	832 (23.97)	851 (24.14)	896 (24.97)	983 (26.92)	950 (25.68)	0.0606	0.002
Total population	3120260	3255820	3371734	3471559	3525386	3587879	3651625	3699761		
51-60 years										
Case number	1057 (63.00)	1104 (63.63)	1167 (64.36)	1085 (57.09)	1262 (61.94)	1328 (61.17)	1668 (72.23)	1679 (68.18)	0.887	0.234
Total population	1677838	1734999	1813109	1900623	2037599	2171028	2309311	2462760		
61-70 years										
Case number	1861 (135.96)	1925 (140.01)	2080 (149.84)	2035 (144.88)	2082 (146.34)	2154 (149.33)	2528 (172.31)	2557 (172.29)	4.949	0.004
Total population	1368803	1374856	1388121	1404604	1422734	1442460	1467159	1484167		
71-80 years										
Case number	1618 (203.49)	1793 (213.46)	1921 (217.70)	2078 (225.54)	2503 (263.27)	2414 (247.92)	2777 (279.21)	2733 (269.66)	10.96	0.001
Total population	795134	839952	882424	921327	950732	973682	994582	1013491		
> 80 years										
Case number	456 (204.62)	560 (237.54)	667 (266.39)	711 (264.63)	846 (288.94)	927 (292.72)	1110 (328.30)	1218 (336.27)	17.60	< 0.001
Total population	222848	235749	250381	268677	292797	316689	338109	362212		

* Data are given as number of patients and obtained from the Taiwan Cancer Registry Data Base; [#] Age-specific colorectal cancer incidence rate: per 100000 person year.

Simple linear time trend regression was used to distinguish trends over time of colorectal cancer stratified by age group.

women (n = 26,617 [42.9%]) were significantly younger (mean age, 64.3 ± 14.2 years) than men (n = 35,443 [57.1%]; mean age, 65.3 ± 13.2 years; *p* < 0.001) at the time of CRC diagnosis. Among women diagnosed with CRC, 65.4% had colon cancer, a higher percentage than that of men diagnosed with CRC and having colon cancer (62.4%, *p* < 0.001). No differences existed in the histologic distribution between men and women.

In our series, younger CRC patients had a significant percentage of mucinous adenocarcinoma (7.71%) and signet-ring cell carcinoma (2.43%). These findings are similar to those from previous studies conducted on Western populations.³⁻¹³ Moreover, a prior comparison of the characteristics of colon cancer in patients aged 20-40 and 60-80 years reported more mucinous (15.7% vs. 11.5%) and signet cell (3.8% vs. 0.8%) tumors, and a higher percentages of poorly differentiated (27.3% vs. 17.2%) and anaplastic (1.6% vs. 0.7%) tumors in the younger group compared to

the older group.²⁰ Defects in the DNA mismatch repair gene lead to hereditary CRC associated with the Lynch syndrome. Clinically, the Lynch syndrome might be suspected by CRC onset at a relatively early age, excessive synchronous and metachronous CRCs, and specific pathological findings, including tumor-infiltrating lymphocytes, signet ring cells, or a strong mucinous component.^{30,31} Although only 2-5% of all CRCs are associated with the Lynch syndrome, its identification is clinically important, particularly for other family members.^{31,32} In Taiwan, the incidence of Lynch syndrome was 2.3%;³³ however, these Lynch syndrome patients were not excluded from our study and this is the first limitation of this study.

Several studies demonstrated that younger patients have more advanced stages of the disease, more aggressive histopathologic characteristics, and poorer prognosis compared to older patients. The more aggressive pathology and the advanced stage of disease in younger people result in poorer prognosis for

younger patients with colorectal carcinoma. In our study, younger patients (≤ 40 -years-of-age group) had poorer 1-year, 3-year, 5-year overall survival ($p < 0.001$) and cancer-specific survival ($p < 0.001$) than elderly patients (41-50, 51-60, and 61-70 year groups, shown in Table 3). We have also demonstrated that younger CRC patients in this population study had a significant percentage of mucinous adenocarcinoma (7.71%) and signet-ring cell carcinoma (2.43%). More aggressive histopathologic characteristics were found in the younger CRC group and they may have resulted in the poor prognosis. However, the lack of information on tumor stage, to compare stage-to-stage survival of younger versus older patients with CRC, is the second limitation of this study. We have no evidence to prove whether these differences in prognosis are due to a more advanced stage at presentation.

Many hospitals operate at different volume and experience levels, and surgeons with different skill levels may have been involved. Generally, the prognosis of cancer patients is affected by the surgeon's skills and by the post-operative management. Detailed pathological findings, such as the depth of tumor invasion, lymph node metastasis, lymphatic invasion, venous invasion, and neural invasion, were missing. The rates of postoperative chemotherapy for colon cancer and neoadjuvant chemoradiation for rectal cancer, which are potentially confounding factors, are not available from the databases that we used, and these are other limitations of the study.

Previous studies reported variable outcomes, with some studies showing no differences and others revealing that younger patients do better or worse than older patients. The major discrepancies in the findings between these reports might originate from selection biases in the retrospective studies. Taiwan's National Health Insurance (NHI) system is a social insurance program administered by the government. All citizens, except convicts (who are covered under a separate medical care program), are obligated to participate in the compulsory program. By the end of 2008, 99.48% of the population was enrolled in the program. Due to the unique NHI system providing universal coverage and guaranteed equal access to health care services, the Taiwan Cancer Registry captures nearly all newly diagnosed cancers in Taiwan each

year. Therefore, we performed this population-based study to test whether age differences affect survival in CRC patients.

Evaluating the impact of age differences on survival, when based on data from population-based registries that report mortality rates, may be limited by its inability to correct for prognostic data that affect survival; the latter include stage, mode of presentation, and treatment. Cancer-specific survival lies in the categorization of the cause of death and the reliance on death certificates; the latter have considerable inaccuracies, such as the underreporting of malignancies compared to post-mortem diagnoses.³⁴ The differential classification of the cause of death on death certificates according to age may be a potential confounder.

Conclusion

No increases in colorectal cancer rates are seen, at present, in younger generations in Taiwan. More aggressive histopathologic characteristics, and more poor overall survival and cancer-specific survival were noted in younger as compared to older CRC patients.

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原 著

大腸直腸癌趨勢的國家資料：台灣的人口研究

周家麟^{1,2} 翁世峰^{3,4} 鄭立勤¹ 田宇峯¹

¹奇美醫療財團法人奇美醫院 外科部 一般外科

²台北榮民總醫院 外科部 大腸直腸外科；國立陽明大學

³奇美醫療財團法人奇美醫院 醫學研究部

⁴嘉南藥理科技大學 醫務管理系

目的 在不同年齡層發病的大腸直腸癌預後，目前仍無定論。此篇研究是分析台灣的癌症登記資料來分析，不同年齡層大腸直腸癌的預後差異。

方法 本研究收集了自 1998 年到 2005 年，台灣大腸直腸癌的癌症登記資料。於 1998 至 2005 年間，共有 65113 位診斷為大腸直腸癌，其中 62060 位病患有組織學確定診斷為大腸直腸腺癌、黏液性癌或戒指型細胞癌，收錄在本研究中。將這些病人的病理及存活的資料予以分析。

結果 從 1998 年到 2005 年間，小於 40 歲的大腸直腸癌病患比率，由 6.8% 降到 4.6%。在 2000 年之前，大腸直腸癌主要分布在 51~60 歲和 61~70 歲；2000 年之後，61~70 歲和 71~80 歲躍昇為主要族群。小於 40 歲的大腸直腸癌病患相較於其他年齡層的病患 (41~50 歲、51~60 歲、61~70 歲)，有較高的黏液性癌或戒指型細胞癌的發生率及較差的 1 年、3 年、5 年總體存活率和癌症存活率。

結論 根據國家癌症登記的資料，目前在台灣的大腸直腸癌病患並沒有年輕化的趨勢。小於 40 歲的大腸直腸癌病患有較差的組織學型態，且相較於其他年齡層的病患 (41~50 歲、51~60 歲、61~70 歲) 有較差的預後。

關鍵詞 結腸直腸癌、年紀、預後。