



Colorectal cancer in adolescent and young adults: epidemiology in Japan and narrative review

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Background and Objective: Although only a small proportion of colorectal cancer (CRC) cases develop in adolescents and young adults (AYAs), its incidence has increased recently. We aimed to conduct a narrative literature review and summarize the epidemiology, clinicopathological features, genetics, and treatments for AYA-CRCs.

Methods: We searched the articles published in the PubMed database until November 30, 2022, with keywords, “((adolescent and young adult) OR AYA) AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))” and “young-onset AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))”.

Key Content and Findings: In Japan, the annual incidence of AYA-CRC was approximately 1,200 in the 1970s, but has increased to 2,000 nowadays. An increased incidence of AYA-CRC has also been reported in other countries. AYA-CRC tends to be a more advanced disease at presentation than CRC in older patients, with more adverse histological features and variability in molecular characteristics. Diagnosis of CRC is often delayed in AYAs because they are not invited to undergo cancer screening. Three to five percent of patients with AYA-CRC have hereditary cancer syndromes such as Lynch syndrome and familial adenomatous polyposis (FAP), and a family history should be obtained. Additionally, providing information on fertility preservation and social systems before starting treatment is important for sustainable treatment and life after cancer treatment.

Conclusions: The number of AYA-CRC cases is increasing in Japan. Before initiating treatment for AYA-CRC, we should know that these patients may have a hereditary disease and fertility preservation should be explained. More physicians should be aware of the importance of AYA-CRC.

Keywords: Adolescents and young adults (AYAs); colorectal cancer (CRC); hereditary cancer; epidemiology; screening

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Introduction

In Japan, approximately one million people are diagnosed with cancer annually, 2% of whom are adolescents and

young adults (AYAs) (1). Colorectal cancer (CRC) is the most common cancer and the second leading cause of cancer-related death in Japan; more than 150,000

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patients are newly diagnosed with CRC, and more than 50,000 patients die from CRC every year (2). Among AYA individuals in Japan, CRC is the fourth most common cancer after breast, uterine, and thyroid cancers (3). The incidence of AYA-CRC is up to 2,000 patients per year, accounting for approximately 10% of all cancers diagnosed in this age group (4). In Japan, healthy AYAs are not recommended for cancer screening, except for cervical cancer (5). Cervical cancer screening with cytology is recommended for women aged 20 years or more, though the implementation rate is reported to be low (6). Regarding CRC, a population-based screening program with annual immunochemical fecal occult blood tests was started in 1992 as a national policy; however, this program only targeted people over 40 years of age based on morbidity (7). Thus, it may be difficult to diagnose AYA-CRC at the asymptomatic stage. In addition, failure to recognize or deny the importance of symptoms may lead to a delayed diagnosis (8). A case-control study showed that the median time from symptom onset to treatment was 217 days in patients aged <50 years compared to 29.5 days in patients aged ≥50 years (9). In this article, we aimed to review the clinicopathological characteristics, genetics, and management of AYA-CRC. Although there have been a lot of excellent review articles about young-onset CRC (10–12), most of them do not focus on the AYA population (15–39 years old). As far as we know, this is the first review article that highlights current situations of AYA-CRC in Japan. We present this article in accordance with the Narrative Review reporting checklist (available at <https://jgo.amegroups.com/article/view/10.21037/jgo-23-98/rc>).

Methods

We conducted an electronic search of articles in the PubMed database published until November 30, 2022. Articles related to AYA-CRC were identified using keywords, “((adolescent and young adult) OR AYA) AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))”. We also searched and reviewed articles related to young-onset CRC using keywords such as “young-onset AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))”. Only the articles published in English were included. Articles without abstracts, case reports, and articles without available full text were excluded (Figure 1). When we searched literatures related to young-onset CRC, review articles were also excluded because there was a lot of overlap of information. The entire text of the articles was reviewed and analyzed by

AU. No systematic review of the articles or meta-analysis was performed. The detailed methods are summarized in Table 1. Although the definition of AYA varies among reports (13), we used this term for individuals aged 15–39 unless otherwise specified.

Epidemiology and clinical characteristics of AYA-CRC

Epidemiology of AYA-CRC in Japan and other countries

The incidence of AYA-CRC in Japan is increasing gradually, from 1,200 patients diagnosed with CRC in 1975 to 2,000 in 2015 (Figure 2A) (4). Increasing trends in AYA-CRC have also been reported in other countries such as the United States (14,15), Canada (16), England (17,18), and Australia (19,20), and similar trends have been observed worldwide (21). The Global Burden of Disease Study has reported the global epidemiology of AYA-CRC; the global incidence of AYA-CRC had increased from 37,285 in 1990 to 76,090 in 2019 (22). Recent changes in lifestyles such as Western-style diet and physical inactivity are thought to have caused the increase of the incidence of AYA-CRC (23). In the United States, one in 1,200 (0.08%) individuals developed CRC at 40 years of age or younger in the current era (24); in particular, the incidence of rectal cancer is increasing more rapidly than colon cancer (25). By 2030, it is estimated that the incidence of CRC in individuals aged 20–34 will increase up to 90% for colon cancer and 124% for rectal cancer (26). On the other hand, the incidence of AYA-CRC in Korea between 2011 and 2015 decreased slightly compared to those between 2006 and 2010 (27). A multinational cohort study in Asia showed that the increasing trend of young-onset (including 40–49 age group) was the most pronounced in male rectal cancer (28).

A Japanese multicenter cohort study showed a slight male predominance (56.8%) in the incidence of AYA-CRC with 54.4%, 23.7%, and 21.9% of tumors occurring in the rectum, left colon, and right colon, respectively (29). A single-center study in Taiwan showed that >40% of AYA-CRC cases were stage IV at diagnosis and <10% were stage I at diagnosis (30). The mortality rate of AYA-CRC has decreased in Japan, and the annual number of deaths from CRC has decreased from 700 in 1975 to 250 in 2020 (Figure 2B) (2). In the United States, on the other hand, the mortality of AYA-CRC is still increasing (31,32). Disease stage at diagnosis is the most striking prognostic factor,

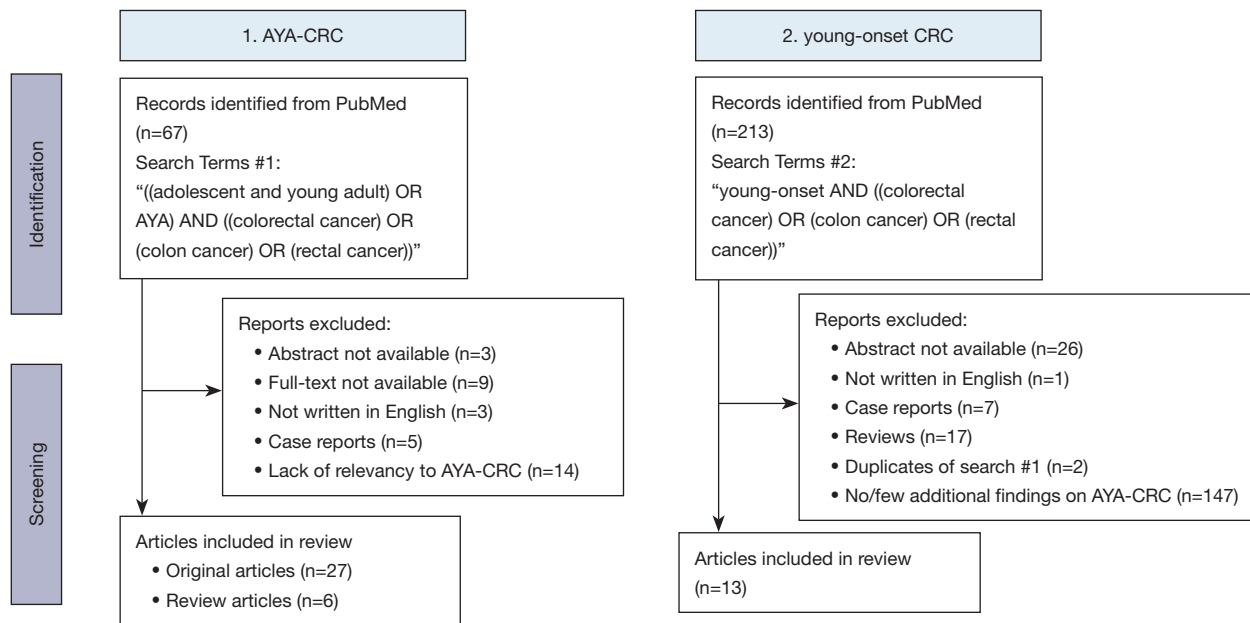


Figure 1 Literature search flow diagram. AYA, adolescent and young adult; CRC, colorectal cancer.

Table 1 The search strategy summary

Items	Specification
Date of search	1 December 2022
Databases and other sources searched	PubMed
Search terms used	#1 “(adolescent and young adult) OR AYA) AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))”; #2 “young-onset AND ((colorectal cancer) OR (colon cancer) OR (rectal cancer))”
Timeframe	Until 30 November 2022
Inclusion and exclusion criteria	Inclusion: English language, abstract, and full-text available. Exclusion: case reports (#1 and #2) and reviews (#2)
Selection process	A Ueno reviewed and analyzed the extracted articles

whereas male sex, black genetic ancestry, no insurance, poorly differentiated histology, higher tumor grade, and exposure to fine particulate matter pollution have also been reported to be associated with worse survival (33-35).

Risk factors for AYA-CRC

Family history of CRC may be an important risk factor for AYA-CRC. Mork *et al.* retrospectively analyzed 193 patients aged 35 years or younger and found that the family history of CRC in first- and second-degree relatives was present in 11.9% and 32.1%, respectively (36). Another study showed

that the presence of a family history of CRC in first-degree relatives increases the risk of CRC by up to 4-fold (37). Understanding the risk factors for AYA-CRC can help identify those who would benefit from CRC screening, and AYAs with a family history may benefit from CRC screening.

According to a recent systematic review, one prospective, five retrospective, and one cross-sectional study investigated the risk factors of young-onset CRC, five of which targeted the AYA population (38). Due to the rare incidence of AYA-CRC, three studies investigated the risk factors for adenomas or other neoplastic polyps and identified family

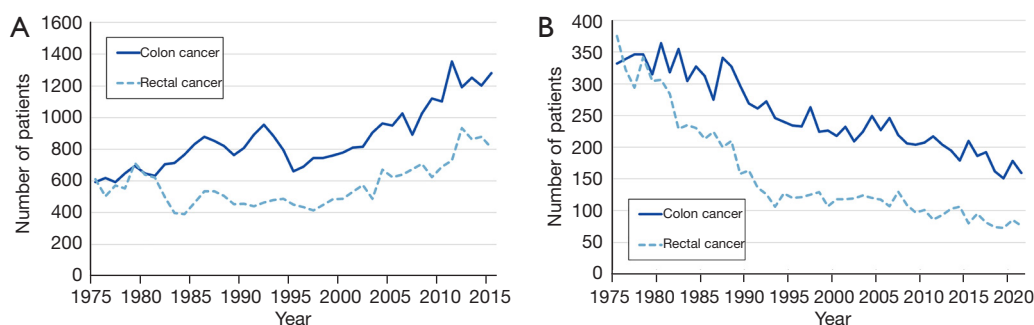


Figure 2 Longitudinal change of estimated (A) annual incidence and (B) annual mortality of colorectal cancer in people aged 15–39 years in Japan.

history of CRC, older age, male sex, obesity, less physical activity, smoking, alcohol intake, and diabetes mellitus as risk factors for neoplastic colonic polyps in AYAs (39–41). On the other hand, two studies assessed the risk factors for CRC or rectal cancer in AYAs and revealed that family history of CRC, genetic ancestry other than black or white, and inflammatory bowel disease were associated with a higher frequency of AYA-CRC (42,43). The risk factors and associated evidence are summarized in Table 2. Kim *et al.* pointed out that several risk factors such as smoking, drinking, and less physical activity can be changed and maintaining good lifestyle habits would help prevent AYA-CRC (39). In a large cohort of female nurses aged 25–42 years, higher intake of vitamin D was associated with decreased risk of early-onset CRC; thus, vitamin D intake may be encouraged in young women (44).

The difference in clinicopathological and molecular characteristics between AYA-CRC and elderly CRC

Several clinicopathological differences have been reported between AYA-CRC and CRC in elderly patients. Adverse histology is more common in AYA-CRC patients than in older patients. In a Japanese multicenter study, 10.2% of resected AYA-CRC cases had mucinous or poorly differentiated histology (29). Another study from the United States revealed that 37% of patients with CRC aged <30 years had poorly differentiated tumors (45). According to the Surveillance, Epidemiology, and End Results database, histopathological diagnoses other than adenocarcinoma were more frequent in patients aged 15–19 (26.7%) than in those aged 35–39 (13.6%) (46). Although most AYA-CRC cases are diagnosed at an advanced stage, the disease-specific and overall survival rates are comparable to or

may be better than those of the general population with CRC (17,47).

Regarding genetic and molecular characteristics, Tricoli *et al.* conducted a comprehensive study using whole-exome sequencing and found that several mutations were significantly more frequent in AYAs with CRC than in patients with CRC aged 61–90 years (48). McVeigh *et al.* evaluated the genomic profile of AYAs with advanced solid tumors and found that a considerable proportion of patients had targetable mutations (49). Salem *et al.* compared the molecular profiles of right- and left-sided CRC in AYAs (50). They found that mutations in *MSH2* and *MSH6*, as well as the microsatellite instability (MSI)-high phenotype, were more frequent in right-sided AYA-CRC than in left-sided AYA-CRC (20.8% *vs.* 4.8%); clinical significance of *MSH2/MSH6* mutations and MSI-high phenotype is described in the following section. Chemotherapy regimens for CRC need to be tailored based on the MSI status; for example, adding oxaliplatin to fluoropyrimidine is recommended as adjuvant therapy for MSI-high CRC (51), and immune checkpoint inhibitors are recommended for stage IV MSI-high CRC (52,53). Therefore, MSI testing should be considered for AYAs with CRC, especially those with right-sided tumors. The consensus molecular subtype (CMS) is a recently developed classification system for CRC at the gene expression level (54), and it has been reported that CMS1 was the most common in the AYA age group (55).

Hereditary cancer associated with AYA-CRC

Although most cases of AYA-CRC are sporadic, approximately 30% are thought to have a hereditary component (37,56). While 3–5% of these have well-characterized hereditary cancer syndromes such as

Table 2 Risk factors for CRC or neoplastic colorectal polyps in AYAs

Risk factors	Description	Reference
Family history	Family history of CRC was associated with an increased risk of NCP (OR, 13.28; 95% CI: 5.70–30.97) Family history of CRC was present in 27% (17/62) of patients ≤ 30 years old with CRC	(40,43)
Age	Age over 30 years was associated with an increased risk of colorectal adenoma (OR, 2.37; 95% CI: 1.64–3.42) Higher age was associated with an increased risk of NCP (OR, 1.11; 95% CI: 1.07–1.15) Higher age was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.09; 95% CI: 1.08–1.11)	(39–41)
Male sex	Male sex was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.37; 95% CI: 1.27–1.49)	(39)
Race	Race other than black or white was associated with an increased risk of rectal cancer in AYAs (OR, 1.46; 95% CI: 1.23–1.73)	(42)
Obesity	Higher BMI was associated with an increased risk of NCP (OR, 1.07; 95% CI: 1.03–1.12) Obesity was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.26; 95% CI: 1.19–1.34)	(39,40)
Less physical activity	Regular exercise was associated with decreased risk of NCP in young adults aged 30–39 years (OR, 0.89; 95% CI: 0.81–0.97)	(39)
Smoking	Current smoking status was associated with an increased risk of colorectal adenoma OR, 1.48; 95% CI: 1.14–1.91 Current or former smoker was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.29; 95% CI: 1.21–1.38)	(39,41)
Alcohol	Alcohol consumption was associated with an increased risk of colorectal adenoma (OR, 1.29; 95% CI: 1.03–1.63) Alcohol consumption was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.25; 95% CI: 1.17–1.33)	(39,41)
Diabetes mellitus and metabolic syndrome	Diabetes mellitus was associated with an increased risk of NCP (OR, 2.80; 95% CI: 1.06–7.42) Metabolic syndrome was associated with an increased risk of NCP in young adults aged 30–39 years (OR, 1.33; 95% CI: 1.21–1.46). Elevated blood pressure (OR, 1.25; 95% CI: 1.16–1.35) and elevated triglyceride levels (OR, 1.24; 95% CI: 1.16–1.33) were also associated with an increased risk of NCP	(39,40)
Inflammatory bowel disease	Underlying inflammatory bowel disease was present in 15% (9/62) of patients ≤ 30 years old with CRC	(43)

CRC, colorectal cancer; AYA, adolescent and young adult; NCP, neoplastic colonic polyps; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Lynch syndrome, familial adenomatous polyposis (FAP) and other rare syndromes including *MutYH*-associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis, polymerase proofreading-associated polyposis and Cowden/PTEN hamartoma syndrome (Table 3), other hereditary cases remain unexplained (57,58). Patients with these genetic backgrounds tend to develop CRC earlier. In most hereditary CRC syndromes, polyps precede the development of carcinoma, but the exact route to carcinoma seems to differ among

the conditions (59). Pearlman *et al.* have analyzed the prevalence of germline mutations associated with cancer susceptibility among 450 CRC patients younger than 50 years, and they revealed that 16% of patients had genetic cancer susceptibility (60). Thus, genetic testing should be considered for all AYAs with CRC (61), although only a few AYA-CRC patients do not undergo such tests in real-world practice. Details of the two most common syndromes, Lynch syndrome and FAP, are reviewed in this section, and comprehensive descriptions of other syndromes are

Table 3 Hereditary syndromes associated with AYA-CRC

Syndrome	Responsible genes	Frequency	Lifetime risk of CRC	Average age at CRC diagnosis (years)	Clinical characteristics
Lynch syndrome (hereditary nonpolyposis CRC)	<i>MLH1, MSH2, MSH6, PMS2, EPCAM</i>	2–5% of all CRC	50–80%	40–45	Right-sided, locally advanced tumors Microsatellite instability-high phenotype Commonly associated with various extracolonic cancers
FAP	<i>APC</i> on chromosome 5q21	1–2% of all CRC (1:10,000–20,000)	Almost 100%	39	>100 adenomatous polyposis with average onset before 20 years old Polyposis also found in the stomach and duodenum
MutYH-associated polyposis	<i>MutYH</i>	About 1% of all CRC	35–53%	35–45	Broad clinical spectrum sometimes resembling attenuated FAP
Peutz-Jeghers syndrome	<i>STK11</i>	<1% of all CRC (1:25,000–300,000)	39% by age 70 years	60	Commonly associated with extracolonic cancer Melanocytic macules on lips, perioral, and buccal regions
Juvenile polyposis syndrome	<i>MADH4 (SMAD4/DPC4), BMPR1A</i>	<1% of all CRC	17–68% by age 60 years	35–45	Hamartomatous polyposis throughout the gastrointestinal tract
Polymerase proofreading-associated polyposis	<i>POLE, POLD1</i>	<1% of all CRC	Reported to be 80% in a small study	35–40	Sometimes associated with endometrial, breast, and/or brain tumors Good response to immune checkpoint inhibitors
PTEN hamartoma tumor syndrome (Cowden syndrome)	<i>PTEN</i>	<1% of all CRC	9–16%	40s	Lifetime risks for a variety of cancers such as breast, thyroid, kidney, and skin cancer

AYA, adolescent and young adult; CRC, colorectal cancer; FAP, familial adenomatous polyposis.

available in the guidelines of the Japanese Society for Cancer of the Colon and Rectum (58).

Lynch syndrome

Lynch syndrome is the most common hereditary syndrome associated with CRC. It is caused by germline mutations in mismatch repair genes, such as *MLH1*, *MSH2*, *MSH6*, and *PMS2*, and is inherited in an autosomal dominant manner (62). These mismatch repair proteins correct DNA replication errors and they are essential to maintain

genetic stability (63). In Lynch syndrome, mismatch repair deficiency (dMMR) accelerates mutation accumulation and increases the risk of carcinogenesis. dMMR-associated cancer usually shows high tumor mutation burden and MSI-high phenotype (63). *EPCAM* is located upstream of *MSH2*, and mutations in *EPCAM* can be another cause of Lynch syndrome. Hypermethylation of *MLH1* can cause sporadic dMMR/MSI-high CRC, but this condition is not considered Lynch syndrome. In individuals with Lynch syndrome, the lifetime risk of CRC development is estimated to be 50–80%, and CRC is diagnosed between 40

and 45 years of age on average (37). Two teenage siblings with multiple adenomas and CRC have been reported who had heterozygous variants in *PMS2* and *POLD1* (57). *POLD1* mutations are also known as a cause of hereditary CRC (64); thus, the coexistence of these variants may have accelerated cancer predisposition. The Amsterdam criteria have been used to identify those at risk of Lynch syndrome; however, the sensitivity of these criteria is only 78%; thus, Lynch syndrome should be suspected in young patients with CRC and CRC patients with a history of other cancers, even if they do not meet the Amsterdam criteria (65). The Amsterdam criteria has been revised in 1999 (66); however, its mutation detection rate was not improved enough compared to the original criteria (67). Mutations in *BRAF* are found in up to 12% of metastatic CRC and *BRAF* V600E mutations are associated with the female sex, right-sided and advanced CRC, and high mutation burden (68), but these mutations are rare in patients with Lynch syndrome; thus, *BRAF*-specific immunohistochemistry may be useful to exclude Lynch syndrome (69). Some patients with clinical suspicion of Lynch syndrome and MSI-high tumors lack pathogenic mutations in the mismatch repair gene; these patients are defined as having mutation-negative Lynch syndrome or Lynch-like syndrome (58). Lynch syndrome-related CRC tends to be mucinous, high-grade, and right-sided (70). More than 80% of CRC cases in patients with Lynch syndrome demonstrate an MSI-high phenotype (45). Other cancers associated with Lynch syndrome include endometrial, gastric, small bowel, hepatobiliary, urinary tract, ovarian, and brain tumors. When a brain tumor arises in patients with either Lynch syndrome or FAP, they are considered to have Turcot syndrome (71). Individuals with confirmed or suspected Lynch syndrome should undergo colonoscopy for CRC screening every 1–2 years, beginning at the age of 20–25 years, which has been shown to reduce mortality risk (72,73). Surveillance of other cancers, including uterine, ovarian, gastric, and urinary tract cancers, should also be considered (73,74).

FAP

FAP is the second most common hereditary syndrome associated with AYA-CRC, occurring in 1/17,400 individuals (58). FAP is caused by a loss-of-function mutation in the *APC* gene. Hundreds to thousands of polyps arise throughout the large bowel and the lifetime risk

of CRC approaches 100% in the absence of prophylactic colectomy. The median age for the development of CRC is 35–40 years in these patients (58). Approximately 80% of all causes of death in FAP patients was CRC until the 1980s; however, the proportion has been decreasing to approximately 60% since the 1990s. Among extracolonic manifestations, desmoid tumors and duodenal cancer are the leading causes of death, with incidences of approximately 10% and 6%, respectively (75). Patients with FAP should undergo surveillance with sigmoidoscopy or colonoscopy every 1–2 years beginning at 10–11 years of age (73). Owing to a large number of polyps and the high risk of CRC, patients with classic FAP should undergo prophylactic surgery in their 20s (37,58).

Special consideration in the treatment of AYA-CRC

Chemotherapy regimens

It is essential to test for MSI status before administering chemotherapy to patients with AYA-CRC because they are more likely to have MSI-high tumors, as mentioned in the previous section; MSI-high CRC requires different treatment strategies from microsatellite stable tumors. However, it remains unknown whether the optimal treatment for AYA-CRC differs from that for CRC in elderly patients. Kneuertz *et al.* reported that young patients (aged <50 years) with CRC received significantly more postoperative chemotherapy but gained only a minimal gain in survival (76). These findings cannot be simply interpreted because MSI status was not assessed in this study, but we should be aware that more intensive treatment may not always be beneficial. In addition, while young patients are less likely to develop severe neutropenia than their older counterparts, the frequency of nausea is higher in young patients (77). For metastatic diseases, no age-related differences in the efficacy of chemotherapy have been reported (78). Nonetheless, all previous studies were limited by their study design or sample size; therefore, further research with an adequate number of patients with AYA, ideally randomized controlled trials, will be required to clarify the optimal treatment for AYA-CRC.

Fertility preservation

Fertility is a significant concern for AYAs diagnosed with cancer. The total fertility rate has been reported to be lower in female CRC survivors than in the general population (79).

Adhesions after pelvic surgery, radiotherapy, and systemic chemotherapy can cause infertility. Chemoradiotherapy for rectal cancer is associated with a high risk of infertility in female patients, whereas most standard chemotherapy regimens are associated with an intermediate-to-low risk (80). The risk of chemotherapy-induced infertility seems to differ according to the chemotherapy regimen; 5-fluorouracil (5-FU) is believed to cause a temporary reduction in sperm count in men but has a low risk of causing amenorrhea in female patients, whereas oxaliplatin has been suggested to have moderate gonadal toxicity (81). Various fertility preservation options can be offered to AYA patients with cancer. The Japan Society of Clinical Oncology has published clinical practice guidelines for fertility preservation that recommend embryo (fertilized oocyte) cryopreservation for female patients with a male partner (grade B), unfertilized oocyte cryopreservation for female patients without a partner (grade C1), ovarian tissue cryopreservation for female patients who require urgent cancer-directed therapy or in whom ovulation induction is difficult for oocyte harvesting (grade C1), and sperm cryopreservation for male patients (grade B) (82). Because up to 88% of male patients experience sexual dysfunction after surgery for rectal cancer (83), nerve-sparing surgery is recommended when there is a risk of erectile or ejaculatory dysfunction (82). The role of fertility preservation should be informed to patients before surgery, pelvic radiation, and/or chemotherapy (74). However, in a case series from the United States, only 20% of young women (aged 18–45 years) with CRC received fertility counseling (84). In a recent international cross-sectional study, approximately half of the young patients with CRC (aged <50 years) discussed reproductive health with their healthcare providers (85). In Japan, fertility preservation is often provided for patients with breast or hematologic cancer, but rarely for patients with CRC (86). Physicians who treat AYA-CRC patients should also explain fertility preservation to patients before treatment.

Survivorship

Owing to the increased incidence and improved mortality of AYA-CRC, the number of young CRC survivors is likely to increase in the coming decades. Survivors are at risk of CRC recurrence, second primary cancers, and the long-term adverse effects of CRC and anticancer treatment and may suffer from psychological, reproductive, genetic, social, and employment concerns. Thus, special attention

is needed for AYA-CRC survivors who have completed active anticancer treatment (87). Previous studies have shown that AYA-CRC survivors (≥ 2 years after diagnosis) have a 2.83-fold (95% confidence interval: 2.23–3.59) higher risk of hospitalization than their siblings or matched general population (88). Because approximately 20% of patients with AYA-CRC develop a secondary primary neoplasm within 35 years, surveillance for a second primary malignancy may be required and the second cancer tends to be diagnosed within five years after the primary cancer diagnosis (89–91). CRC is the second most common cancer after AYA-CRC, followed by cervical and thyroid cancers (89). On the other hand, stomach, liver and bile, and pancreas cancers were reported to be leading causes of secondary cancer-related deaths (92). In addition, it has been reported that the health-related quality of life of AYAs with CRC is low, even in nonmetastatic patients (93). Returning to work is sometimes challenging for CRC survivors (94,95), and a large questionnaire-based study revealed that 25% of young cancer survivors were unemployed (96). Psychosocial support and networking through AYA patient communities will play an important role because these patients may have limited life experiences and underdeveloped coping skills (97). Especially, male patients aged <50 years were reported to have a higher risk of mental health disorders after diagnosis of CRC compared to average-age CRC patients (98). Several studies on survivorship models for patients with AYA-CRC have been reported; however, evidence of their effectiveness is lacking (99). Moreover, most phase III therapeutic trials of AYAs in cancer have not included patient-reported outcomes (100). Future studies focusing on the quality of life of AYA-CRC survivors are warranted.

Future perspectives for early diagnosis of AYA-CRC

Educational strategies are needed to increase the awareness of patients, primary care physicians, and gastroenterologists to reduce the delayed diagnosis of AYA-CRC. First, AYAs should be informed that they can develop CRC and that the initial symptoms may be rectal bleeding, weight loss, changes in bowel habits, abdominal pain, and/or iron deficiency anemia (74,101,102). Second, all physicians should consider screening for CRC in all AYAs complaining of the above symptoms, especially if they have a family history of CRC (74). Finally, early detection of CRC in asymptomatic AYAs remains a challenging issue because

population-based CRC surveillance for AYAs has not been justified in terms of cost-effectiveness. However, every AYA in Japan can undergo individual opportunistic cancer screening with out-of-pocket payment. Increased AYA-CRC awareness may encourage AYAs to engage in out-of-pocket CRC surveillance, as reported for breast cancer screening (103). Kwak *et al.* prospectively evaluated the prevalence and characteristics of colorectal adenomas in 4,286 asymptomatic young adults (aged 20–39 years) and found that 0.9% of the participants had advanced adenomas (41). In particular, individuals aged >30 years, current smokers, and alcohol drinkers had a significantly higher risk of developing adenomas. In a recent cross-sectional study, the prevalence of colorectal neoplasia in AYAs who underwent colonoscopic screening was 14.9% (104). This information will help AYAs decide whether to perform out-of-pocket CRC surveillance to avoid AYA-CRC-related deaths. We found that only a few studies have been reported from Japan; thus, further research is warranted.

Conclusions

The incidence of AYA-CRC has increased in Japan and other countries. The diagnosis of AYA-CRC is often delayed in current practice; thus, it is necessary for patients, primary care physicians, and gastroenterologists to consider and check for malignant disease, even in AYA patients. AYA-CRC tends to have an unfavorable histology and more advanced disease at diagnosis than CRC in older patients. Up to 5% of AYA-CRC cases are associated with well-described hereditary cancer syndromes; therefore, genetic testing should be considered for all AYAs with CRC. Fertility preservation and survivorship are also important, and adequate explanations and care should be provided to patients with AYA-CRC before and after treatment.

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Ethical Statement: The authors are accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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