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Colorectal Cancer in Australian Young Adults

ABSTRACT:

Purpose of Review: Although the overall incidence and mortality rates of colorectal cancer (CRC) have been decreasing in Australia over the last 20 years, there has been a significant increase in the incidence of early-onset CRC (EOCRC) without a clear explanation. In this review, we have outlined the epidemiology, suggested risk factors, clinicopathological and molecular features, survival and prognosis, and treatment approach for Australian young adults with CRC.

Recent findings: There has been a shift in the epidemiology of bowel cancer incidence and mortality across different age groups, and there are clinicopathological and molecular feature differences between EOCRC and late onset CRC (LOCRC). EOCRC is more common in the distal colon and rectum. Young patients are diagnosed at more advanced stages of the disease with increased prevalence of aggressive pathologic features and tend to receive more aggressive chemotherapies. EOCRC patients present with a predominance of symptoms in the left side of the colon, and importantly, cases do not have clinically known risk factors. The microbiota may play a significant role in the CRC pathogenesis through an impact on host metabolism and through the transmission of metabolic and even CRC risk in non-Mendelian familial aggregation.

Summary: The increase in the incidence and mortality rates of young adults with CRC has been significant. Thus, more collaborative research is needed to explain the reasons behind the increase in CRC incidence, and to identify young adults in the population at an increased risk of developing CRC at an early age.

Keywords: Colorectal Cancer; Early-onset CRC; Late-onset CRC; Incidence and Mortality rates; Risk Factors.

Abbreviations: CRC: Colorectal Cancer; EOCRC: Early-Onset CRC; LOCRC: Late-Onset CRC; LS: Lynch Syndrome.

INTRODUCTION

In Australia, colorectal cancer (CRC) was estimated to be the most frequently diagnosed digestive-tract cancer in 2018 and was Australia's most frequent digestive-tract cancer killer [1]. CRC is the third most commonly diagnosed cancer and the second leading cause of cancer death worldwide [2]. The age distribution, however, has altered with an increase in incidence of early-onset CRC (EOCRC) being reported in Australia, the USA and many other developed countries [3-9]. There is a difference in the literature regarding the exact definition of early onset as different researchers have used various age groups including individuals under

30, 35, 40, 50 or 55 years, and therefore findings of various studies are difficult to be compared and interpreted [10-24]. However, in general these studies show the increase in the incidence of CRC in young adults. A study published in 2019 found that CRC incidence has increased by almost 10% in individuals under 50 years of age since 1990 in Australia [25]. Between 1990 and 2010, the incidence of CRC increased by 85% to 100% in Australian aged 20-29 years and by 35% in the age group 30-39 years [26]. In 2018, as many as 14% of all new CRC cases and 10% of all Australian who died from CRC were <55 years [27]. In 2019, CRC is estimated to be the third most commonly diagnosed cancer in Australians aged 25-49 years [28]. In contrast, there has been a remarkable decrease in the overall prevalence of CRC in individuals above the age of 50 years (LOCRC) since the 1990s [29-32]. The increase in EOCRC incidence is not well explained; some researchers recommend that colonoscopy screening age for people with normal risks should be lowered from 50-45 years. However, those young adults who are under the age of 45 years will not benefit from this recommendation and this does not address efforts to explain why the incidence and mortality rates of CRCs have been increasing in young adults [33]. This review will explore the epidemiology, suggested risk factors, clinicopathological and molecular features, survival and prognoses, and treatment approach for Australian young adults with CRC.

Epidemiology of EOCRC

CRC is largely a disease of older patients, with an average age at diagnosis in Australia of 69 years [34]. Screening not only detects cancers but also detects advanced pre-cancerous polyps in the ratio of four to five lesions for every one cancer detected, thus facilitating both prevention and early detection [35]. In the USA, colonoscopy screening is now recommended at 45 instead of 50 years of age for individuals at normal risk for developing bowel cancer [36]. In Australia, under the guidelines individuals under the age of 50 years are not included in the target age range for the National Bowel Cancer Screening Program (NBCSP) [37]. This program, increasing awareness of the need to screen for bowel cancer, and advances in cancer therapy, have likely caused a significant decrease in both the incidence and mortality rates of LOCRC [32,38]. The global analysis of CRC temporal trends shows a decrease in incidence and mortality rates of this disease in all ages combined over time in Australia. In contrast, the incidence and mortality rates of EOCRC have been increasing, when the analysis is stratified into specific age groups, over the last two decades in Australia, the USA, and other countries with similar overall trends of this disease **(Figure 1)** [32,38]. The incidence of CRC has increased 186% in individuals between the ages of 15-24 years in the last three decades [27] and it is considered to be the most common cancer-related cause of death for those aged 25-29 [15]. In addition, Feletto et al., recently analysed over 375,000 cases of colon and rectal cancers from 1982 to 2014 in Australia. This study confirms that the incidence rates of colon cancer has increased in young adults under the age of 50 years since the mid-2000s, with the increase in the annual percentage changes (APCs) ranging from 1.7% to 9.3% per annum depending on specific age group. The incidence rates of rectal cancer has also increased among the same group of ages from the 1990s, with the increase in the APCs ranging from 0.9% - 7.1% per annum [32]. The data shows that early-onset CRC is a current public health concern in the USA, Australia [23,27,39] and in other countries[3-9] **(Table 1)**.

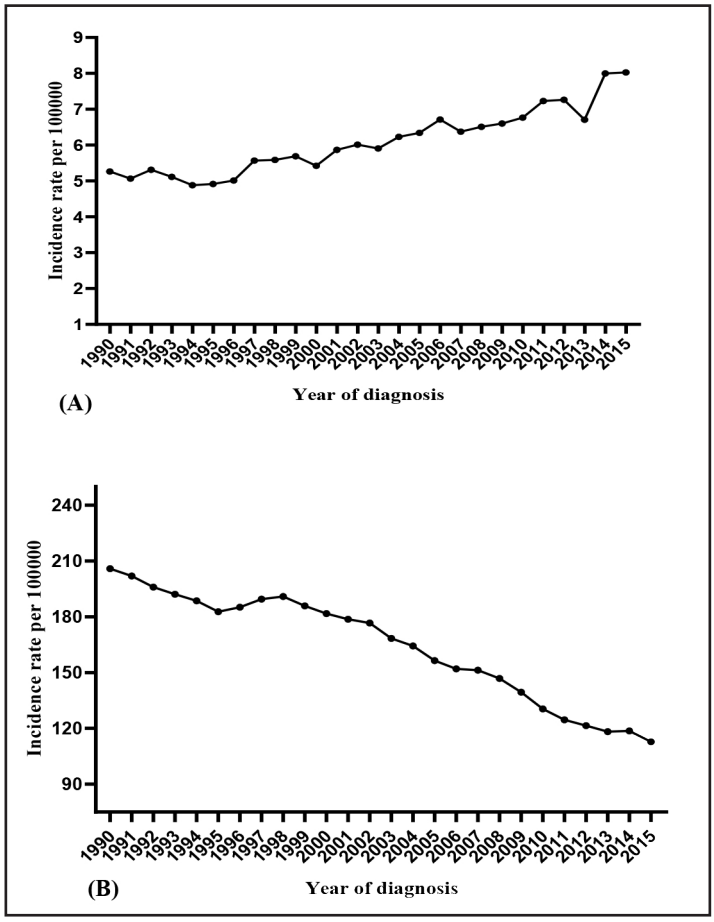

Figure 1: Age-adjusted SEER incidence rates of CRC from 1990 to 2015 among people under and above 50 years of ages in the USA. Graph (A) shows the incidence of CRC in people under the age of 50 years. Graph (B) shows the incidence of CRC in people above the age of 50 years. (https://seer.cancer.gov/faststats/selections.php?#Output).

Table 1. The prevalence of early-onset CRC in different countries.

Country	Early-onset CRC	Age of onset	Reference
Pakistan	52%	Under 40 years	[40] [41]
India	39%	Under 40 years	[42]
Iran	36%	Under 40 years	[43]
Nigeria	31.50%	Under 40 years	[44]
Nepal	28.60%	Under 40 years	[45]
Egypt	25%	Under 40 years	[46]
Korea	22.40%	Under 50 years	[47]
Jordon	20.20%	Under 40 years	[48]
Turkey	20%	Under 45 years	[49]
Sri Lanka	19.70%	Under 40 years	[50]
Taiwan	18.80%	Under 50 years	[51]
Saudi Arabia	17%	Under 40 years	[52]
Australia	14%	Under 55 years	[27]
Singapore	14%	At or under 55 years	[53]
Canada	10%	Under 50 years	[54]
USA	10%	Under 50 years	[55]
UK	5%	Under 50 years	[56]

The prevalence of CRC is not uniform across all racial and ethnic groups, though there is an increase in the prevalence of this disease across the entire population. This variation in proportion of CRC occuring at an earlier age may reflect the expected lifespan of these sub-group in particular countries, as well as genetic background and a greater sensitivity to Western lifestyle risk factors **(Table 1)**. For example, in the USA, incidence rates were reported to be higher among African Americans aged between 20-40 years than non-Hispanic Whites [57]. In New Zealand, even though the death rates of young-onset CRC were similar among Pacific, non-Mâori non-Pacific and Mâori people by 1996-99, the death rates had accelerated up to 10-fold among Pacific people, by 50% among Mâori and decreased by 10% to 20% among non-Mâori non-Pacific people during 1981 to 1995 [58].

Among Australians aged 15-24 years from 2010 to 2014, CRC ranked as the fifth and fourth most commonly diagnosed cancer in males and females, respectively [27]. The incidence of CRC is slightly higher in males which accounts for 53% of cases under the age of 55 years in Australia [15]. Weir et al., reported that Aboriginals are significantly younger than non-aboriginals when diagnosed with CRC (17% compared to 6% of EOCRC) and are more likely to have diabetes or other chronic diseases [59]. It is notable that studies vary in the exact proportion of anatomical distribution of the primary site of CRC (sometimes described by exact site or right vs left vs rectum). However, regarding EOCRC, there does seem to be a consensus that there is an increased prevalence in the distal colon and rectum [22,60-65]. By contrast, proximal colon tumours are more predominant within LOCRC patients [23,63,64,66]. This variation in incidence by anatomical sites have made scientists suggest to separate risk factors for colon versus rectal cancer. These anatomical subistes are different in terms of embryological origins, level of oxygenation, concentration of bile salts and the microbial enviroment [67].

Hereditary and Family High-Risk of CRC Cases

It is reported that up to 30% of bowel cancer patients have a strong family history of the disease, and 5% of those are due to a demonstrable inherited genetic abnormality [68]. Compared to individuals without a family history of CRC, people with a first-degree family history of CRC have two to four times the risk of developing this cancer [69]. In Australia, 16% of CRC patients have at least one first-degree relative with bowel cancer [70]. However, this figure is lower in Sweden and Finland as ~11% to 13% of all CRC cases have at least one first-degree relative with CRC [70-72]. Hereditary and family history risk factors can induce the development of EOCRC and form a group of people with higher risk relative to the general population who should be under closer cancer surveillance [73]. However, given that hereditary CRC is under closer surveillance in current times, it is unlikely that this group of patients are responsible for the increase in incidence in EOCRC.

Lynch syndrome (LS) is the most frequently diagnosed of the EOCRC inherited syndromes, accounting for up to 17% of all CRC cases [74] **(Tables 1 and 2)**. It is defined as an autosomal dominant cancer predisposition syndrome which is caused by germline mutation in one of the four mismatch repair (*MMR*) genes (*MSH2, MLH1, MSH6*, and *PMS2*) **(Table 2).** Germline mutations in the *MLH1* and *MSH2* account

for approximately 70% to 90% of the LS cases [75,76] while mutations in *MSH6, PMS2* are detected in 10% to 20% of LS cases [77]. With the loss of activity of DNA MMR enzyme, there is accumulation of multiple mutations which facilitate cancer growth and metastasis, as well as leading to manifestations of microsatellite instability (MSI). An alternative silencing cause for *MSH2* and leading to LS is a germline deletion in the epithelial cell adhesion molecule (*EPCAM*) gene which is located upstream of *MSH2* [78]. *EPCAM* germline mutations are reported to account for 6.3% of all LS cases [79]. This germline deletion results in silencing the transcription of *MSH2* by causing its allele-specific methylation. Therefore, the risk of bowel cancer in patients with *EPCAM* germline mutations (75%) is similar to those with MSH2 mutations (77%) by the age of 70 years [80]. The clinicopathological features associated with CRCs in LS include poor tumour differentiation, proximal location, mucinous histology, lymphocytic reactions, and synchronous and metachronous lesions [81,82]. People with LS have a 70% lifetime risk of susceptibility to CRC [83] **(Table 2).** In addition, a recently identified Lynch-like syndrome (LLS) has been described where there is an MMR-deficient colorectal tumour without germline mutations and/or *MLH1* promoter methylation, and it can be as frequent as 70% of suspected LS patients [84].

Approximately 35% to 45% of LS cases are diagnosed with CRC before the age of 40-45 years, and this syndrome accounts for approximately one-third of EOCRC in people under the age of 30 years [74,82,85,86]. However, the average age at bowel cancer diagnosis among people with LS syndrome is 42-45 years **(Table 2)**. Rarey, bi-allelic deleterious mutations of MMR genes result in constitutional mismatch repair deficiency. This condition predisposes patients to CRC, among other cancers, with an average age of 16 years at the time of diagnosis which is much earlier than LS [87-90].

Familial Adenomatous Polyposis (FAP) is the second most frequently diagnosed autosomal dominant inherited syndrome (less than 1%). Clinically, classic FAP is characterized by the development of numerous (hundreds to thousands) adenomatous polyps in the bowel, appearing from the age of 10-12 years **(Table 2)**. Patients with this syndrome have a 100% lifetime risk CRC by the age of 40 years if prophylactic colectomy is not performed. However, the median age at CRC diagnosis among people with FAP syndrome is around 39 years [91] **(Table 2)**. Germline mutations in adenomatous polyposis coli (*APC*) gene is an early event in the progression of FAP and is the main cause of the classic and attenuated FAP (*AFAP*) syndromes [92] **(Table 2).**

Table 2. Summary of the main hereditary and familiarly high risk CRC syndromes.

Syndrome	Inheritance	Gene	The average age of CRC diagnosis	CRC lifetime risk factor	Incidence in EOCRC	Clinicopathological features
LS	Dominant	*MLH1, MSH2, MSH6, PMS2, EPCAM*	40-45	70%	17%	Poor differentiation carcinoma, mucinous carcinoma, tumour-infiltrating lymphocytes and more commonly found in the right colon.
FAP	Dominant	*APC*	39	100%	< 1%	Good differentiation carcinoma, no mucinous carcinoma, no lymphocytic reaction and more commonly found in the distal colon.
MAP	Recessive	*MUTYH*	48	43-100%	<1%	Development of 10 to 100 adenomatous polyps in the colon and rectum
SPS	Unknown	Unknown	55-65	<50%	<1%	Multiple and/or large serrated polyps throughout the colon and rectum.

LS: Lynch syndrome, **FAP**; Familial Adenomatous Syndrome, **MAP**: MUTYH-Associated Polyposis, **SPS**: Serrated Polyposis Syndrome.

MUTYH-Associated Polyposis (MAP) is another subtype of polyposis which has an autosomal recessive transmission, and is related to bi-allelic germline mutations in the mutY DNA glycosylase (*MUTYH*) gene [93]. MAP patients have a lifetime risk of developing CRC of 43% to 100%, at an average age of 48 years, with about 50% of cases presenting with cancer at the time of diagnosis [94,95]. The phenotypes of AFAP and MAP syndromes are often indistinguishable. There are currently,

no exact phenotypes of the MAP condition. Some reports show one single CRC and no or less than ten polyps, or cases presenting with mostly hyperplastic/serrated polyps [96], while proximal adenomas are also commonly seen. Moreover, the cancers related to MAP syndrome are more likely to be found in the proximal side of the colon in comparison to the AFAP related tumours [95]. Germline mutations in the *MUTYH* have also been reported in patients with LLS **(Table 2)**.

Another syndrome of CRC predisposition is serrated polyposis syndrome (SPS). SPS is under recognized and is characterized by the presence of many serrated polyps in the colon and rectum [97]. Boparai et al., found CRC in 35% of individuals with SPS, with the majority of cases (94.5%) being diagnosed with CRC at the time of SPS diagnosis. However, 6.5% of patients were under surveillance for SPS while diagnosed with CRC [98]. Currently, 40% to 60% of SPS patients demonstrate a family history of bowel cancer rather than of polyposis. Nevertheless, it is worth noting that the exact patterns of inheritance of this syndrome are still not clear, and autosomal recessive alleles and autosomal dominant alleles are suggested [99,100] (**Table 2**). SPS accounts for a currently unknown proportion of EOCRC.

Risk Factors and Microbiota

Different lifestyle-related risk factors including obesity and diabetes have been associated with the significant increase in the prevalence of EOCRC (**Table 3**). In Australia, the prevalence of obesity and overweight have increased [101], and from 1985-2012, childhood obesity has also grown among Australian's children [102]. The proportion of Australians aged 18 years and over, who were obese or overweight, has increased since 1995, and 46% of adults aged 18-24 were obese or overweight in 2017-2018, and this had increased to 68.7% by age 35-44 years [103]. According to the available data, though red meat consumption has decreased since the 1970s in Australia, it remains above 1 kg per week (32). Also, adults in Australia consumed over 11 g of processed meat daily in 2011-2012 (32). Australia is amongst the highest in the OECD (95 kg in 2016) in terms of meat consumption per capita [104]. Smoking and lack of physical activity have also been associated with a higher risk of developing CRC (32). However, in Australia, smoking has deceased across all age groups since 1995 with the largest decline in individuals aged between 18-34 years [103]. Nevertheless, though some risk factors for CRC in young adults have increased in parallel to the increase in EOCRC, and an independent relationship is yet to be clearly demonstrated. Nguyen et al., has recently reported a significant association between increased risk of EOCRC and sedentary TV watching time after adjusting the persumed risk factors such as lack of exercise and obesity [105]. Additionally, there is a consistent relationship between type 2 diabetes and CRC, and this is likely to be more pronounced in young adults under 55 years [106]. In summary, lifestyle factors involving activity level and metabolism issues are the most liekly contenders for the increase in the incidence of EOCRC.

Table 3: Some factors associated with the risk of colorectal cancer (CRC).

Risk factor	Higher risk percentage	Author
Inflammatory bowel diseases (IBDs)	People with IBDs have a two to threefold higher risk of developing CRC.	[107]
Diabetes mellitus	Higher risk of developing CRC compared to general population (HR, 1.3, 95%CI 1.2-1.5).	[106]
Solid Organ Transplantation	The increase of proximal colon tumour (SIR=1.69, 95%CI: 1.53–1.87).	[108]
Appendicitis	Appendicitis patients have a higher risk of CRC (SIR 4.6, 95% CI 4.0-5.2; SIR 3.5, 95% CI 2.9-4.1).	[109]
Physical Inactivity	Least active individuals are by 27% at higher risk of susceptibility to CRC.	[110]
Obesity	Obese or overweight women have double the risk of developing bowel cancer under age 50 years compared to healthy body weight women.	[111]
Meat Consumption	Red meat and processed meat increase the risk of CRC by 30% and 20%, respectively.	[112]
Fibre	Swedish women with a high intake of vegetables and fruits had 32% risk reduction for bowel cancer.	[113]
Calcium	T risk of CRC was about 70% lower in people with the highest consumption of Ca+2 compared to people with the lowest calcium intake.	[114]

Vitamin D	There was a considerably lower risk of developing CRC in people with a high blood level of vitamin D (1,25(OH)2D3) and high lymphocyte accounts.	[115]
Alcohol	A modest increased risk of colon tumour (45%) and rectal tumour (49%) with regular high intake of alcohol (>45 g/day) in both genders combined in relative non-drinkers.	[116]
Smoking	Smokers were 2-fold at higher risk of advanced neoplasia than non-smokers, similar to or higher than those patients that have the first-degree relative with this disease.	[117, 118]

The microbiota may play a role through impacting on host metabolism, and through the transmission of metabolic and even CRC risk factors in non-Mendelian familial aggregation, as has been shown in co-housed preclinical animal models [119]. Obesity and diabetes, and CRC itself have been linked to changes in the gingival and gut microbiota in humans. Though there have been multiple findings suggesting causation in animal models, a number of confounding factors such as genetic background, and stress may have played a role. It is currently not definitively known whether these observations are readily translated into human settings and whether human studies suggest direct causation or setting-associated colonisation in a predisposed host. For example, findings in humans of insulin sensitivity being improved in obese subjects after faecal transplantation into the small intestine from lean donors [120], indicate that microbiota in the obese do not necessarily cause obesity, but that a certain element of the microbiota from lean individuals lacking in the obese can modify insulin sensitivity. Similarly, obese patients who experienced weight loss had improved response to periodontal therapy over those who remained obese with persisting gum disease [121,122], could be interpreted as setting-associated. The composition of bacteria chronologically alters as people age, as well as depending on location within the bowel [123,124]. Some species of bacteria have been recognized to have a role in investigating bowel cancer pathogenesis such as *Bacteroides fragilis, Fusobacterium nucleatum*, *Streptococcus bovis*, and some strains of *Escherichia coli*. Findings of studies in older CRC patients showed a significant role of F. *nucleatum* in the pathogenesis of CRC, particularly in the right-side cancers [124]. Other studies found that F. *nucleatum* travels as bowel cancer metastasizes in mice, and murine cancers with this bacterium respond to the metronidazole antibiotic [125]. However, while it can be postulated that microbiota might be involved, there is not yet much convincing evidence in an area which is difficult to research. Also, it is currently not known whether the microbiota has a role in EOCRC.

Survival rate, Prognosis and Clinical Features of EOCRC

The overall 5-year survival rate of CRC for all stages combined from diagnosis is approximately 69% in Australia [126] and 60% in the USA [30,127]. Considering all stages of the disease the 5-year survival rate of CRC has increased by 18% between 1985-1989 and 2010-2014 in Australia [126]. In 2007, Quah et al., reported that the outcomes (recurrence rates and 5-year survival) of CRC stages I, II, III were similar, if not better, between EOCRC and LOCRC patients. In particular, there were no noticeable differences in the local and distant recurrence rates between the groups (17% vs 18%). Moreover, there were no differences in the 5-year recurrence-free survival between EOCRC (80%) and older patients (79%) after four years and eight months of following up. Finally, the overall relative survival rate in older patients (73%) was worse than in EOCRC patients (84%) [14,128]. In 2004, O'Connell et al., reported that the 5-year survival rate, when matched for stage, was the same for stage I and II between EOCRC and LOCRC patients, but it was substantially higher in younger individuals for stage III and IV disease [12]. In contrast, a retrospective analysis, including nine phases III trials, reported that progression-free survival- but not response rate or overall survival- was higher among EOCRC patients (<40) compared to LOCRC patients [129].

It has been reported that approximately 86% of EOCRC cases are symptomatic at the time of diagnosis [60]. Symptoms are often non- specific, such as abdominal pain, fatigue or weight loss; but EOCRC patients also tend to have a predominance of the symptoms in the left side including a change in the bowel habits and rectal bleeding [12] (**Figure 2**). In addition, EOCRC compared to LOCCRC patients more frequently present with symptoms of abdominal pain (41.2 vs 27.2%) and hematochezia (28.8 vs 23.2%) [130]. However, although CRC in young adults is often symptomatic, diagnosis is generally delayed possibly because of the lack of awareness of the increasing incidence of early-onset CRC [131]. It has reported that the majority of EOCRC cases at the time of diagnosis were already distantly metastatic or regionally advanced, as they tend to present with more aggressive pathological features [10,14,22,61,64-66,132-143]. In addition, mucinous and signet ring features

are more common in EOCRC patients than in LOCRC patients [64,66,135,140,144-146]. Chang et al., reported that CRC patients at and under the age of 40 years tend to have higher signet features compared to late-onset CRC patients (13% vs 1%), higher perineural invasion (29% vs 11%) and higher venous invasion (22% vs 6%) [147]. Studies have shown that tumours with mucinous and signet ring features are associated with a negative prognostic factor, poor differentaition, and more advanced tumour stages [148-153].

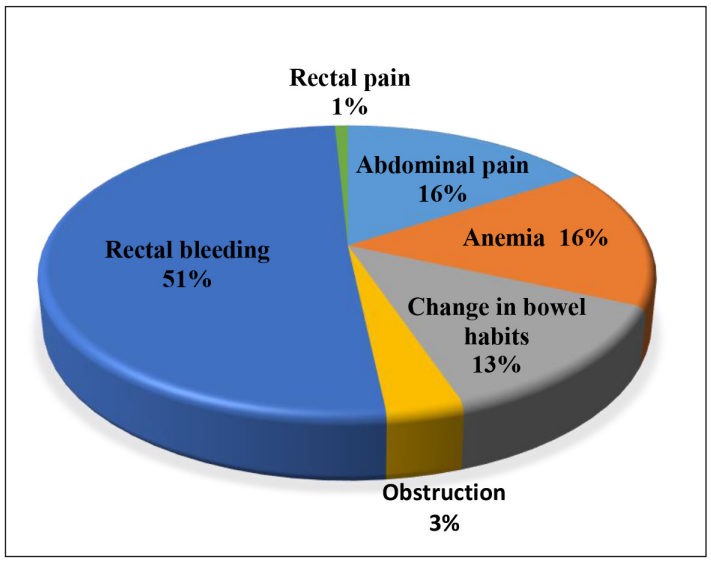

Figure 2: Presenting symptoms of CRC patients aged under 50 years old (Adapted from [154]).

Molecular Characteristics of Sporadic EOCRC

Approximately 65% of CRC is sporadic with no apparent hereditary genetic predispositions or family history [154,155]. Though EOCRC raises the likelihood of a hereditary predisposition, only the minority of CRC cases in young adults (15% to 20%) are due to the hereditary syndromes [60,156], which is slightly higher than all CRC cases (2% to 8%) [157]. Among EOCRCs and in the general population, the adenoma-carcinoma pathway contributes to the development of approximately 85% of all CRCs. In contrast, evidence has shown that about 15% to 30% of CRCs exhibit the features of an alternative serrated neoplasia pathway [158-160]. There are three underlying molecular mechanisms which have been described in the development of CRC: chromosomal instability (CIN), microsatellite instability (MSI) and CpG methylator phenotype (CIMP) [161]. These three mechanisms are not mutually exclusive and may overlap in some subsets of CRC [158-162].

CIN, which accounts about 85% of sporadic CRCs [163], is characterized by continuing errors in chromosomal segregation including a high rate of gains or losses of whole chromosomes or large fractions of chromosomes [164]. This results in aneuploidy, rearrangement of chromosomes, copy number variations, as well as mutations in tumour suppressor genes and oncogenes such as *APC*, *TP53, KRAS* and *BRAF* which subsequently contribute to CRC carcinogenesis [156-166]. In general, the genome of EOCRC patients is more frequently euploid and hypermethylated than LOCRC cases [167,168]. Somatic mutations of the *KRAS* gene are found in about 35% to 45% of CRCs [169] and predict a lack of response to anti-EGFR targeted therapy [170-172]. In EOCRC, the incidence of KRAS mutations remains questionable, with the incidence of these mutations ranging from 4% to 54% in EOCRCs [144,146,147,173-176]. Similarly, *BRAF* mutations in EOCRC are reported to range from 0% to 14.3% [143,144,177-181]. In addition, loss of the chromosomal regions coding for loci, where *APC, SMAD4* and *DCC* genes, is more common in LOCRCs than EOCRCs [182-184]. In contrast, EOCRCs lose the chromosomal regions which code for CRC markers (TJP2) [185-187] and FOX transcriptional factors [188], and gain regions coding for AMP-kinase regulatory subunit and *BMPR1A* [185]. Puccini et al., reported that mutations in genes such as *KDM5C, KMT2A, KMT2D* and *SETD2* which are involved in the modification of histones are higher in EOCRCs than LOCRC.

MSI-H, which represents ~21% of the EOCRC, is characterized by the inability of the MMR system to maintain the DNA structure or to correct errors during the process of DNA replication as well as by accumulation of point mutations and changes in the repetitive microsatellite nucleotide sequences [146,147,173,175]. MSI-H cancers in EOCRC are mostly linked to LS, with some cases having epigenetic inactivation of *MLH1* and wild-type *BRAF* which are categorized as epimutation-type LS. CIMP has been shown to contribute to approximately 40% of all CRCs and is involved in the alternative serrated neoplasia pathway [155,189]. This pathway is categorized by high methylation of CpG islands and early *BRAF* mutations. Hypermethylation of the MMR gene *MLH1* is also frequently reported in this pathway, and can result in diploid CRCs that are MSI. Tumours which are CIMP-high are usually found in the right-side colon, have high-MSI, a higher rate of *BRAF* mutations and are poorly differentiated. CRC with CIMP and *BRAF* that are MSI-H are mostly observed in LOCRC. Tumours which are CIMP-low are also observed in young adults with CRCs [190].

Studies have consistently shown that the prevalence of *KRAS/RAS* and *BRAF* mutations, as well as MSI, is higher in right-side colon tumours than left-side [191-194]. This is clinically relevant given survival benefits with selective anti-EGFR inhibitors are higher in patients with left-side *RAS* wild-type colon tumours compared to the individuals with proximal colon tumours. The differing prevalence of primary site may lead to survival implications based on age. For female EOCRC estrogen may play a role as some studies have suggested that estrogen might be a protective factor for the development of CRC in the proximal colon. As its level decreases with age, this may result in the increasing prevalence of proximal colon tumours in female adults above the age of 50 years [195]. Evidence for this hypothesis comes from reports that women with higher estrogen exposure were more protected against high-MSI cancers which are very often found in the proximal colon [196]. However, a tumour mutational burden (TMB) is more frequent in young adults with left-sided colon tumour than their older counterparts (9.7% vs 2.8%, P<0.001). TMB may have relevance to immunotherapy options for this group of patients [197]. For example, although RAS WT is higher in left-sided cancer, there is a higher rate of *HER2* amplification and NF1muattions in young adults with left-sided colon tumour than older individuals [197] which may have clinical relevance. Therefore, though there is a difference in the proportion of mutations between EOCRC and LOCRC, this may reflect, at least in part, the different site distrubution of CRC between the two age groups.

Treatment

CRC patients are generally treated in a standardized way based on current guidelines [198,199]. Sporadic CRC in individuals younger than 50 years may have a different molecular profile, and treatment may differ based on this [136,197,200,201], but ultimately the therapeutic strategy will be guided by the exact profile rather than age. There are subtle but real differences that may reflect age. For example, guidelines allow choice of first-line systemic chemotherapy schedules, which may vary from single-agent fluoropyrimidine to triplet therapy (FOLFOXIRI), although in general doublet chemotherapy is recommended [202]. However, data from registries do suggest that young adults with CRC tend to receive more aggressive chemotherapies compared to older patients with this disease. This is probably because these patients can tolerate more aggressive regimens and the misconception that EOCRC patients have worse treatment outcomes. EOCRC patients more commonly receive adjuvant therapy more often with multi-agent adjuvant regimens. Despite this trend, there is little evidence this improves outcome significantly. For example, Kneuertz et al., showed no survival gain in their analysis for patients diagnosed with stage II CRC (RR, 0.90; 95% CI, 0.69-1.17). A minor survival benefit may exist for those diagnosed at stages III-IV (RR, 0.89; 95CI, 0.81-0.97) [136]. However, further evidence is required to which subgroups may benefit most [150]. Surgical intervention does appear to differ by age, with resection of primary cancer more commonly performed in young adults with metastatic CRC (mCRC) compared to older mCRC patients (70.8% versus 66.6%; P < 0.001) [14,203-205]. Resection of primary may impact on the outcome by preventing future complications [204-206] and may impact on survival [145,204,205,207-210].

EOCRC patients are also more likely to undergo radiation therapy in the setting of metastatic rectal cancer than their older counterparts [14]. Radiation therapy for the rectal primary in metastatic disease is used to control the local recurrence rate. There are few studies regarding the recurrence rate of rectal cancer in young adults compared to their older counterparts after radiation therapy. However, You et al., reported that the recurrence incidence of the tumour was higher in young adults with rectal cancer, especially distant metastasis than their older counterparts after a similar length of following up [211]. In addition, Fossum et al., conducted a retrospective review comparing patients with synchronous resectable lung or liver metastasis who did not receive neoadjuvant therapy versus those who received neoadjuvant therapy. It was found that none of the patients who received neoadjuvant therapy had a local recurrence after follow up of 43 months while 26% of patients without neoadjuvant therapy had a local recurrence (P<0.001) [212].

CONCLUSION

EOCRC incidence is increasing in Australian and has some different clinicopathological and molecular features in comparison to LOCRC, largely related to the higher prevalence of genetic predisposition, and the increased prevalence of distal colon and rectal primary site. While the American Cancer Society has lowered the screening age to 45 years, Australians under 50 years of age are still not included in the target age range for the NBCSP. EOCRC is a heterogeneous disease, the majority of the cases are

sporadic and there are no identified risk factors, though various lifestyle-related factors and gut microbiota might have contributed to this significant increase. While the pathogenesis of inherited CRC syndromes in young adults is well explored, the molecular features of sporadic EOCRC are not robustly explained. More collaborative research is needed for a better explanation of the molecular features of EOCRCs. Molecular features may play a role in understanding for development of EOCRC as they may reflect the sentinel risk factors which trigger this condition. A better understanding of the molecular characteristic differences between EOCRC and LOCRC may also facilitate personalized medicine in the treatment of EOCRC in the future.

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