



# Familial and non-familial risk factors associated with colorectal cancer survival in young and middle-aged patients

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## Abstract

**Background** Survival following colorectal cancer (CRC) survival may be influenced by a number of factors including family history, individual medical history, and comorbidities. The impact of these factors may vary based on the patient's age.

**Methods** The study cohort consisted of individuals born in Western Australia between 1945 and 1996, who had been diagnosed with CRC prior to 2015 ( $n = 3220$ ). Hospital, cancer, and mortality data were extracted for each patient from state health records and were used to identify potential risk factors associated with CRC survival. Family linkage data, in combination with cancer registry data, were used to identify first-degree family members with a history of CRC. The association between survival following CRC diagnosis and identified risk factors was examined using Cox proportional hazard models.

**Results** Age and sex were not significantly associated with survival in young patients. However, in middle-aged patients increasing age (HR 1.03, 95% CI 1.01–1.05,  $p = 0.003$ ) and being male (HR 0.72, 95% CI 0.60–0.87,  $p < 0.001$ ) were associated with reduced survival. Being diagnosed with polyps and having a colonoscopy prior to CRC diagnosis were associated with improved survival in both young and middle-aged patients, while a history of non-CRC and liver disease was associated with reduced survival. In middle-aged patients, having diabetes-related hospital admissions (HR 1.53, 95% CI 1.15–2.03,  $p = 0.004$ ) was associated with reduced survival.

**Conclusions** In both young and middle-aged patients with CRC, factors associated with early screening and detection were associated with increased CRC survival while a history of liver disease and non-CRC was associated with decreased CRC survival.

**Keywords** Colorectal cancer · Survival · Family history · Risk factors · Young · Middle-aged

## Background

Colorectal cancer (CRC) accounts for almost 10% of cancer diagnoses worldwide, and is the fourth most common cause of

cancer-related death [1]. Encouragingly, CRC mortality is decreasing in the European Union, North America, Australia, and New Zealand [2–4], particularly in young and middle-aged persons [4]. CRC survival is largely dependent on the

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stage of diagnosis, with 5-year survival rates ranging from 90% in patients diagnosed at the localized stage, to 10% for patients with distant metastatic cancer. In keeping with this, tests that result in early detection, such as colonoscopy and fecal occult blood testing have been shown to reduce CRC mortality [5, 6].

Middle-aged and older patients make up the majority of patients diagnosed with CRC, with 90% of patients aged 50 years and over at the time of first diagnosis [7]. As such, screening programs are generally not undertaken in patients under the age of 50 years. A lack of routine screening means that young CRC patients are often diagnosed at a later cancer stage. Additionally, young patients are more likely to have poorly differentiated tumors that are associated with poorer outcomes [8]. Despite this, survival in young patients is comparable with older patients [9, 10], perhaps due to better overall health resulting in faster post-operative recovery and higher tolerance for chemotherapy [11].

CRC location has been shown to influence survival following diagnosis. Distal colon and rectal cancers have been associated with increased survival compared with proximal colon cancer [12]. The distribution of CRC locations in young patients differs from older patients, with a higher percentage of rectal tumors and a lower percentage of proximal colon cancers in young patients [13, 14]. Family history of CRC appears to be more strongly associated with the risk of proximal colon cancer compared with rectal cancer [15].

In addition to screening, stage, and anatomic location, a number of lifestyle and demographic factors are associated with CRC survival. In women, low physical activity, high body mass index, and smoking have been associated with reduced survival [16]; however, these risk factors were not significantly associated with survival in men with CRC [17]. Low socio-economic status, single marital status, low education, and unemployment were found to be associated with poor survival in both sexes [18]. However, the impact of medical factors such as family history, individual medical history, and comorbidities on survival following CRC diagnosis is not currently well understood. Additionally, it is unclear how these factors affect survival in patients of different ages, particularly given differences in the etiology of CRC in young and middle-aged patients. The objective of this study was therefore to examine the impact of these factors on CRC survival from a population-based sample of young and middle-aged individuals in Western Australia (WA).

## Methods

### Study design and cohort

The study was a population-based retrospective cohort study. The study cohort consisted of all individuals born

in WA between 1945 and 1996, who were diagnosed with CRC at 18 years or older. The study cohort was stratified into two age groups: young (18–49 years at diagnosis) and middle-aged (50–69 years at diagnosis) patients. The study utilized state-wide data sets that were linked by the WA Data Linkage Branch using probabilistic-matching methods [19].

### Data sources

The WA Birth Registry (1945–1996) and Midwives Notification System (1980–1996) were used to identify individuals who had been born in WA between 1945 and 1996. The WA Cancer Registry (1980–2014) and the WA Death Registry (1969–2014) were used to identify individuals who had been diagnosed with CRC prior to the 31st of December 2014. Individuals diagnosed with CRC before the age of 18 were excluded from the study. ICD codes used to identify participants with CRC are outlined in Supplementary Table 1.

For patients with CRC, demographics, family history, comorbidities, and medical history were taken from other state records. Demographic data (age and sex) were taken from a combination of the WA Birth Registry and/or Midwives Notification System records and verified using data from the hospital, cancer, and death registry, with disparities resolved using the most common reported value.

A family history of CRC was determined using the Family Connections System, which was used to identify all first-degree relatives (i.e., parents, children, and siblings). Family members were then matched with data from the WA Cancer Registry, Hospital Morbidity Data Collection (HMDC), and WA Death Registry to identify diagnoses of CRC.

Medical history and comorbidities were obtained for each individual from the HMDC. Each HMDC record contained a principal diagnosis and up to 20 additional diagnoses, using International Classification of Diseases (ICD) coding (version 8, 9, and 10) and up to 11 procedure codes. Details of the diagnosis and procedure codes and their timeframes are included in Supplementary Table 1. Candidate risk factors for CRC survival from these data included known risk factors for CRC (e.g., inflammatory bowel disease (IBD), polyps), diseases associated with poor overall health (e.g., diabetes, liver disease, and alcohol-related diagnoses), and procedures associated with CRC diagnosis (e.g., colonoscopy). Data on prior non-CRC diagnoses were collated from the WA Cancer Registry and HMDC data. Full details of the diagnosis and procedure codes used to identify risk factors are included in Supplementary Table 1.

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## Data analysis

Age, sex, cancer location, and family history were summarized using frequencies and proportions for the whole cohort and separately for the two age groups. Comparisons between the two age groups for sex, percentage with a first-degree relative with CRC, and CRC location (proximal or distal) were made using univariable logistic regression. One-year and 5-year survival for all-cause and CRC-related mortality were calculated for patients with sufficient follow-up (at least 1 or 5 years of follow-up) and were expressed as a percentage. Comparisons between young and middle-age survival were made using univariable Cox proportional hazard models.

Potential risk factors influencing survival following CRC diagnosis were assessed using univariable Cox proportional hazard models, truncated at 5-year follow-up. The analysis was performed for the whole cohort and separately for the two age groups. Candidate risk factors included age, sex, family history of CRC (first-degree relatives), procedure history (e.g., colonoscopy), and co-morbidities/medical history. A multivariable Cox proportional hazard model was created using backward elimination, with a *p* value cut-off of 0.300 for inclusion in the initial model, and *p* critical value of 0.05 for the final model.

All statistical analyses were performed in Stata/MP 14.1.

## Results

### Demographics

The cohort consisted of 3220 adult patients diagnosed with CRC, who were born between 1945 and 1996 in Western Australia. The average age at diagnosis was 51.6 ( $\pm 10.0$ ) years, with 33.2% aged 18 to 49 and 66.8% aged 50 to 69 (Table 1). A total of 362 patients (11.2%) had a first-degree relative who had also been diagnosed with CRC. Middle-aged patients were more significantly likely to be male than young patients. However, the two age groups were not significantly

different in terms of the location of the cancer or the percentage with a family history of CRC.

### Survival

In CRC patients with at least 1-year of follow-up ( $n = 2961$ ), 89.9% were alive at the end of 1 year (Fig. 1). All-cause survival at the end of 1 year was significantly lower in young patients compared with middle-aged patients (HR 0.72, 95% CI 0.57–0.90,  $p = 0.004$ ), with 87.7% of young patients and 91.0% of middle-age patients alive at 1 year. Similarly, CRC survival was significantly lower in young patients compared with middle-aged patients (HR 0.51, 95% CI 0.39–0.66,  $p < 0.001$ ). CRC deaths made up 88.8% of deaths in young patients and 62.9% of deaths in middle-aged patients after 1 year of follow-up.

For patients with 5 years of follow-up ( $n = 2089$ ), 63.6% were still alive at 5 years, with 66.0% of young and 62.1% of middle-aged patients surviving (HR 1.12, 95% CI 0.96–1.30,  $p = 0.139$ ). CRC was the cause of death for 74.2% of patients who died within 5 years of diagnosis. There was no significant difference between 5-year CRC survival in young (86.2%) compared with middle-aged (67.4%) patients (HR 0.87, 95% CI 0.74–1.03,  $p = 0.112$ ).

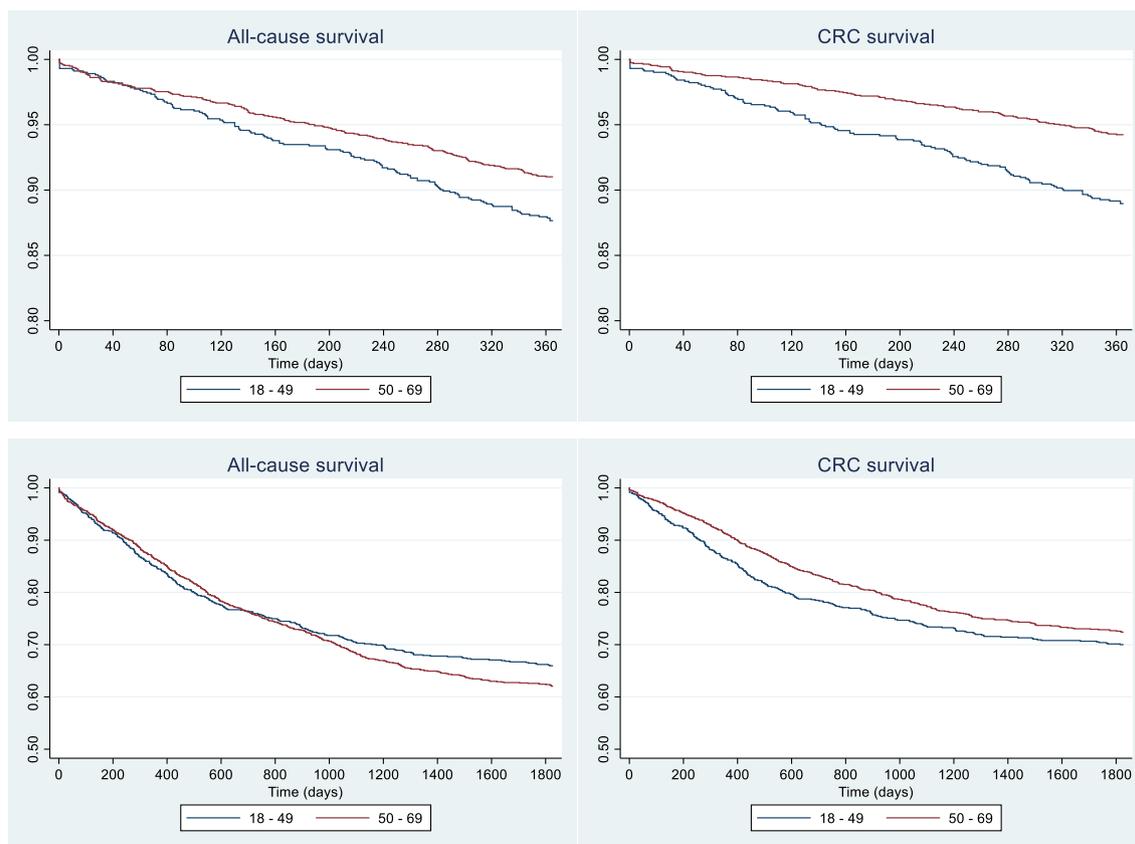
### Risk factors

In the univariable models, all-cause survival following CRC diagnosis was significantly higher in female patients compared with male patients (Table 2), overall and in middle-aged patients. However, in young patients, there was no significant difference between the sexes. The association between age and CRC was different in young and middle-aged patients. In young patients, increasing age was associated with a 2% reduction in hazard, while in middle-aged patients a 3% increase per year was observed. A history of tobacco use was associated with a reduction in survival in middle-aged patients, but not in young patients.

**Table 1** Characteristics of patients diagnosed with CRC, who were born between 1945 and 1996 in Western Australia, overall and stratified by age

	All individuals	18–49	50–69	<i>p</i> value <sup>1</sup>
Number	3220	1069	2151	–
Sex (male), <i>n</i> (%)	1894 (58.8%)	584 (54.6%)	1310 (60.9%)	0.001
Age, mean $\pm$ sd	51.6 $\pm$ 10.0	40.2 $\pm$ 7.2	57.3 $\pm$ 5.2	–
First degree relative, <i>n</i> (%)	362 (11.2%)	105 (9.8%)	257 (12.0%)	0.073
CRC location, <i>n</i> (%)				
Proximal	803 (24.9%)	251 (23.5%)	552 (25.7%)	0.228
Distal	2350 (73.0%)	789 (73.8%)	1561 (72.6%)	
Unspecified	67 (2.1)	29 (2.7%)	38 (1.8%)	

<sup>1</sup> Comparison between young and middle-aged patients using univariable logistic regression



**Fig. 1** One-year (top) and 5-year (bottom) all-cause (left) and CRC (right) survival following CRC diagnosis in young and middle-aged patients

Overall and in middle-aged patients, survival rates were significantly lower in patients with a proximal CRC compared with patients with a distal CRC. However, there was no significant difference in young patients. Conversely, having any first-degree relative diagnosed with CRC was not significantly associated with survival overall or in middle-aged patients, but was associated with a 43% improvement in survival in young patients. This increase was not associated with any particular first-degree relative.

Diagnosis of polyps significantly increased survival, with 78.6% of patients diagnosed with polyps prior to their CRC diagnosis alive at 5 years compared with 51.3% of patients who were not diagnosed with polyps. Similarly, colonoscopies were associated with a significantly increased survival. All-cause survival was significantly reduced for patients with hospital admission for diabetes, alcohol, liver disease, or non-CRC diagnosis prior to CRC diagnosis, both overall and in middle-aged patients. In young patients, history of liver disease and non-CRC was associated with decreased survival; however, diabetes and alcohol were not significantly associated with survival. Rates of all-cause survival significantly improved with time, increasing at a rate of 3–6% per year.

In the multivariable model (Table 3), middle-aged female patients had higher all-cause survival rate compared with middle-aged male patients; however, there was no difference

between young female and male patients. Similarly, while increasing age, smoking and proximal location were significantly associated with decreasing survival in middle-aged patients; in young patients, these variables were not significant in the multivariable model.

Both diagnosis of polyps and previous colonoscopy were associated with increased survival in the multivariable model overall and in each age strata ( $p < 0.001$ ). A history of a hospital admission with a diagnosis of liver disease, and a prior diagnosis of non-CRC was associated with decreased survival in both young and middle-aged patients. In middle-aged patients, being admitted to hospital with a diabetes diagnosis was also associated with reduced survival; however, this was not apparent in young patients. Year of diagnosis was associated with a significant increase in survival, with survival increasing by approximately 5% per year in both young patients and middle-aged patients. Having a first-degree family member diagnosed with CRC was not associated with survival.

## Discussion

Survival rates in this study were consistent with estimates from the USA [20], Australia, and Canada [21]. Both all-cause and CRC survival rates were significantly lower in

**Table 2** Univariable hazard ratios for potential risk factors associated with 5-year all-cause survival following CRC diagnosis, stratified by age

	All patients ( <i>n</i> = 3220)			18–49 ( <i>n</i> = 1069)			50–69 ( <i>n</i> = 2151)		
	%	HR	<i>p</i> value	%	HR	<i>p</i> value	%	HR	<i>p</i> value
Sex (reference: male)	41.2	0.84 (0.73–0.97)	0.021	45.4	0.94 (0.74–1.20)	0.627	39.1	0.78 (0.65–0.94)	0.009
Age (years)	–	1.00 (0.99–1.00)	0.188	–	0.98 (0.96–0.99)	0.003	–	1.03 (1.01–1.04)	0.009
History of tobacco use	31.3	1.31 (1.13–1.52)	<0.001	21.5	0.90 (0.67–1.22)	0.499	36.1	1.57 (1.31–1.88)	<0.001
CRC location (reference: proximal)	73.0	0.78 (0.67–0.92)	0.003	73.8	0.78 (0.59–1.02)	0.071	72.6	0.78 (0.64–0.96)	0.017
Relatives (CRC)									
Any first degree	11.2	0.81 (0.64–1.03)	0.084	9.8	0.57 (0.35–0.92)	0.023	12.0	0.94 (0.71–1.24)	0.653
Mother	4.7	0.68 (0.46–1.01)	0.057	3.8	0.43 (0.18–1.05)	0.063	5.1	0.80 (0.52–1.24)	0.321
Dad	4.7	0.92 (0.65–1.29)	0.617	5.3	0.70 (0.38–1.28)	0.242	4.4	1.06 (0.70–1.59)	0.877
Sibling/s	2.1	0.87 (0.50–1.51)	0.627	1.0	0.31 (0.04–2.19)	0.238	2.7	1.07 (0.60–1.89)	0.822
Child/ren	0.2			Too few values for analysis					
Comorbidities <sup>1</sup>									
Polyps	48.7	0.33 (0.28–0.38)	<0.001	40.5	0.24 (0.17–0.33)	<0.001	52.8	0.37 (0.31–0.45)	<0.001
Inflammatory bowel disease	2.4	1.22 (0.80–1.87)	0.354	4.0	1.37 (0.80–2.34)	0.256	1.6	0.99 (0.49–1.99)	0.974
Diabetes	8.2	1.36 (1.06–1.75)	0.014	3.6	1.19 (0.65–2.17)	0.574	10.5	1.46 (1.11–1.93)	0.007
Alcohol	2.9	1.86 (1.32–2.63)	<0.001	2.4	1.14 (0.54–2.41)	0.736	3.1	2.24 (1.52–3.30)	<0.001
Liver	2.7	2.37 (1.72–3.27)	<0.001	2.3	2.21 (1.21–4.04)	0.010	3.0	2.46 (1.68–3.60)	<0.001
Non-CRC	15.9	1.74 (1.46–2.07)	<0.001	10.0	2.64 (1.95–3.56)	<0.001	18.8	1.52 (1.23–1.88)	<0.001
Procedures									
Colonoscopy	27.1	0.37 (0.30–0.46)	<0.001	23.1	0.29 (0.19–0.44)	<0.001	29.1	0.42 (0.33–0.53)	<0.001
Other									
Year of diagnosis	–	0.96 (0.95–0.97)	<0.001	–	0.94 (0.93–0.95)	<0.001	–	0.97 (0.95–0.99)	0.005

<sup>1</sup> Admitted to hospital with this diagnosis prior to CRC diagnosis

young patients at 1 year, but by 5 years, there was no difference compared with middle-aged patients. The initial reduced survival in young patients may be due to CRC being diagnosed at a later stage and/or the etiology and pathogenesis of early-onset CRC may be distinct from later-onset CRC (as younger patients are more likely to have poorly differentiated

cancers) [22, 23]. After approximately 12–18 months, survival in young patients appears to plateau potentially following the death of terminal patients. After this initial period, young patients appear to do as well or better in terms of survival, perhaps due to young patients being more likely to receive treatment [24] and have superior outcomes associated with

**Table 3** Multivariable hazard ratios for potential risk factors associated with all-cause 5-year survival following CRC diagnosis, stratified by age

	All patients ( <i>n</i> = 3220)		18–49 ( <i>n</i> = 1069)		50–69 ( <i>n</i> = 2151)	
	HR	<i>p</i> value	HR	<i>p</i> value	HR	<i>p</i> value
Sex (base: male)	0.78 (0.67–0.91)	<0.001	–	–	0.73 (0.60–0.89)	0.002
Age (years)	1.01 (1.00–1.02)	0.001	–	–	1.02 (1.00–1.05)	0.020
CRC location (reference: proximal)	0.79 (0.69–0.93)	0.004	–	–	0.72 (0.59–0.88)	0.002
History of tobacco use	1.58 (1.34–1.87)	<0.001	–	–	1.65 (1.35–2.00)	<0.001
Polyps	0.26 (0.22–0.31)	<0.001	0.20 (0.15–0.28)	<0.001	0.29 (0.24–0.36)	<0.001
Diabetes	1.47 (1.13–1.92)	0.004	–	–	1.41 (1.05–1.89)	0.023
Liver	2.46 (1.74–3.47)	<0.001	3.07 (1.66–5.69)	<0.001	2.23 (1.48–3.34)	<0.001
Non-CRC	1.70 (1.41–2.06)	<0.001	2.86 (2.09–3.91)	<0.001	1.46 (1.16–1.83)	<0.001
Colonoscopy	0.29 (0.23–0.36)	<0.001	0.24 (0.16–0.37)	<0.001	0.30 (0.23–0.40)	<0.001
Year of diagnosis	0.95 (0.94–0.96)	<0.001	0.95 (0.94–0.96)	<0.001	0.95 (0.93–0.97)	<0.001

treatment [25]. While survival has been reported to be not significantly different in young and middle-aged patients in previous studies [9, 10], this appears to be dependent on the length of follow-up and to some degree whether survival is examined in terms of all-cause or CRC-related mortality.

In young patients, sex and age were not significantly associated with survival in the multivariable model, while in middle-aged patients, male sex and increasing age were associated with decreased survival. Superior survival outcomes in middle-aged females have been previously reported and persist even when adjusted for prognostic factors such as stage [26–28]. Higher rates of survival in female patients have been observed in a number of other cancer types including melanoma, lung cancer, and non-Hodgkin's lymphoma [29]. It has been suggested that female sex hormones (including hormone replacement therapy) stimulate immunological response slowing the progression of the disease [26]; however, this would not explain the lack of difference in young patients. Difference in phenotypic and genotypic profiles in male and female primary CRC and in young and middle-aged patients may be the driver of the presence and absence of sex difference [28].

The anatomical distribution of CRC did not differ significantly in the two age strata. Overall and in middle-aged patients, there was a survival advantage associated distal CRC compared with proximal CRC. In young patients, there was no significant difference in survival associated with location. Distal CRC are generally considered easier to identify using colonoscopy compared with those located proximally [30] and rates of colonoscopy are generally higher in middle-aged patients, potentially contributing to improved survival in middle-aged patients with distal CRC. Additionally, the symptoms associated with distal disease, e.g., bleeding and altered bowel habits, are more easily identified compared with the proximal condition [31] and these symptoms are more likely to be flagged as a symptom of CRC in middle-aged patients compared with young patients [32, 33].

For young patients, having a first-degree relative diagnosed with CRC was associated with increased survival in the univariable model. However, this was not apparent in older patients or in the multivariable model. The protective effect was likely the result of increased monitoring and early detection of CRC in young patients with a first-degree relative with CRC. Routine monitoring that occurs in middle-aged patients resulting in higher rates of colonoscopy and the inclusion of colonoscopy in the multivariable model (possible association between family history and colonoscopy) may have contributed to no association between family history and survival.

Colonoscopy and the detection of polyps were associated with increased survival across both age groups. The introduction of CRC screening programs involving colonoscopy and fecal occult blood testing has been shown to reduce CRC mortality [5, 6]. The association between polyps and increased survival may be the results of increased screening these

patients. Additionally, patients who have been diagnosed with polyps may have a greater perceived risk of CRC, encouraging them to take preventative measures.

A reduction in survival was observed in middle-aged patients admitted to hospital with a diagnosis relating to diabetes. This diagnosis may be reflective of other indicators of poor health such as elevated body mass index and low physical activity, which have been associated previously with reduced survival in CRC patients [17]. Although increased circulating insulin levels have also been demonstrated to promote cancer cell growth in preclinical models [34], the use of metformin, a medication used to treat diabetes, has been associated with a decreased risk of CRC mortality, perhaps indicating that well-managed diabetes may not be associated with the same risks as poorly managed diabetes [35]. Although we did not have information on insulin control or metformin use in this study, it is likely that our measure (hospitalization due to diabetes) captures predominantly poorly managed diabetes; therefore, our findings may not be extrapolatable to patients with well-managed diabetes who are not presenting to hospital. Similarly, the decreased survival associated with diabetes was only present in middle-aged patients, where the more prominent diabetes is type 2 diabetes; therefore, our results may not be generalizable to type I diabetes.

Liver disease was associated with a reduction in survival in both age groups. A previous study of patients with CRC and liver cirrhosis ( $n = 55$ ) found poorer survival outcomes and higher rates of post-operative complications compared with patients without liver cirrhosis [36], although these outcomes may have been influenced by the fact that fewer patients with liver cirrhosis underwent chemotherapy. In another study, pre-existing liver disease was associated with an increased mortality rate in the 30 days following surgical treatment [37]. Our finding in this much larger study that previous hospitalization with liver disease is independently associated with reduced survival is in agreement with these previous studies.

Colorectal cancer is more common in patients who have previously been diagnosed with a non-CRC, possibly due to an underlying genetic susceptibility to cancer, shared etiologic exposures (e.g., alcohol or cigarette smoking), or as a result of cancer treatments. Given the known increased risk of CRC in people who have been previously diagnosed with a different type of cancer, the decreased survival in this group identified in this study is concerning, as it may indicate patients with a history of cancer are not receiving adequate screening to aid in early diagnosis.

In this study, IBD was not associated with a decreased survival in either age strata. In contrast, a nationwide Japanese study found poorer survival rates in patients diagnosed with both IBD and CRC, compared with CRC alone [38]. A Danish study also found modest reductions in survival in patients with CRC and ulcerative colitis or Crohn's disease [39]. It is generally recommended that

patients with IBD have regular colonoscopies [40], which may have contributed to the lack of association observed between IBD and survival.

Progressive improvements in diagnosis and treatment of CRC were reflected improvements in survival over the study period. Importantly, increased survival was observed in both young and middle-aged patients. Similar trends in CRC survival have also been observed in studies in Europe, North America, Australia, and New Zealand [2–4].

## Limitations

The largest limitation of this study was the lack of information on CRC staging. Staging has a large influence on 5-year survival rate, which is as low as 10% for people diagnosed with distant metastatic cancer, to 90% for cancer diagnosed at the localized stage [41]. Additionally, data on a number of other potentially important risk factors such as body mass index, physical activity, alcohol consumption, diet, and medication use could not be included in the study. Another limitation was that the family history of CRC in this study is likely to be underestimated, as only family members who were diagnosed with CRC within WA would have been included in the study. Our data did not allow chemotherapy to be accurately included in the analysis; therefore, we were unable to investigate or account for the influence of CRC treatment on survival.

## Conclusions

While all-cause 1-year survival is not significantly different in young and middle-aged people, young people were more like to die as a result of CRC compared with middle-aged people. However, by 5 years, there were no significant differences in all-cause or CRC survival.

Early detection via colonoscopy and the identification of polyps play an important role in improving survival in both young and middle-age patients. Medical history and comorbidities such as diabetes and a history of liver disease and non-CRC can be an important indicator of patient survival. However, likely due to increased routine monitoring, comorbidities that are commonly associated with poor survival such as IBD were not associated with poorer survival in this study.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Department of Health Human Research Ethics Committee (2016/02) and reciprocal approval was subsequently obtained from the University of Western Australia Human Research Ethics Committee (RA/4/1/8462).

**Informed consent** A waiver of consent was approved by both ethics committees, as the study met the requirements set out in the National Statement on Ethical Conduct in Human Research (2007).

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