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Familial and non-familial risk factors associated with incidence of colorectal cancer in young and middle-aged persons in Western Australia

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ABSTRACT

Aims: The aim of this study was to examine factors including family history, medical history and comorbidities associated with the risk of colorectal cancer (CRC) in young (18–49 years) and middle-age (50–69 years) individuals.

Methods: State records were used to identify individuals born in Western Australia between 1945 and 1996, and their first-degree relatives. Individuals in the cohort and their relatives were linked to State cancer registry, hospital and mortality data to identify diagnoses of CRC and other risk factors. The associations between CRC and identified risk factors were examined using multivariable logistic regression.

Results: For both young and middle-aged patients, family history of CRC, and a history of smoking, inflammatory bowel disease, liver disease and non-CRC cancer were associated with a significant increase in odds of CRC. In middle-aged patients, having a colonoscopy in the previous 10 years was associated with a reduced odds of CRC regardless of the detection of polyps. However, in young patients only the absence of polyps as confirmed by colonoscopy was associated with a decreased risk of CRC (OR: 0.38, 95%CI: 0.26 – 0.54, $p < 0.001$).

Conclusions: Many of the risk factors associated with CRC were similar in young and middle-aged persons, and should be used to identify high risk young patients for screening. The association between colonoscopy and polyps with CRC was modified by age, likely as the result of routine screening in middle-aged patients.

1. Background

Colorectal cancer (CRC) is more prevalent in older persons, with approximately 90% of patients diagnosed after 50 years of age [1]. As such, screening is generally not indicated before the age of 50 years in most countries [2]. Worldwide, screening programs have been largely successful, reducing the incidence of CRC by at least 4% per year and improving survival rates following CRC diagnosis [3]. However, an increase in the incidence of CRC in patients under the age of 50 years has been observed in more recent years [4–6]. Diagnosis of young people with CRC is often difficult. In young patients, symptoms are often incorrectly attributed to other conditions such as irritable bowel, resulting in diagnoses generally occuring at a later stage [7,8].

Young onset of CRC is more often associated with hereditary cancer syndromes, most commonly familial adenomatous polyposis (FAPs) and hereditary nonpolyposis colorectal cancer (HNPCC), now known as Lynch syndrome [9]. Almost all patients with FAP develop CRC by the age of 40 years unless the colon is removed, while around 80% of all patients with Lynch syndrome are diagnosed with CRC within their lifetime, with the average age of diagnosis in their mid 40's [10,11]. While these syndromes are relatively rare in the general population, with inherited syndromes accounting for just 3–6% of all CRC diagnoses [12], in young patients around 35% of CRC is attributable to a hereditory cancer syndrome [13].

A number of risk factors for CRC have been identified, including non-modifiable risk factors such as sex, inflammatory bowel disease (IBD) (including both ulcerative colitis and Crohn's disease), and type 2 diabetes [14]. Modifiable risk factors such as alcohol consumption, obesity, physical inactivity, smoking, diet (proportion of red meat, vegetables, fruit), and some medications (e.g. nonsteroidal anti-

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inflammatory drugs and post-menopausal hormone therapy) also influence rates of CRC [14]. However, the contribution of these risk factors to the development of CRC in young patients, and particularly how they interact with genetic risk factors, has not been thoroughly examined. Identifying clinically significant risk factors in young patients may help to identify individuals who are at a high risk of CRC and guide screening policy and practice in this population.

The aim of this study was to examine the association between family history of CRC, medical history, and comorbidities and CRC, and how they differ between young (aged 18–49 years) and middle-aged (aged 50–69 years) Western Australians (WA).

2. Methods

2.1. Study design and cohort

The study utilized a retrospective population-level cohort consisting of all individuals born in WA between 1945 and 1996, and examined risk factors associated with CRC using longitudinal linked health data. Analyses were conducted in the overall cohort and in stratified groups of young (aged 18–49 years) and middle-aged (aged 50–69 years) individuals.

2.2. Data sources

Participants were identified through the WA Birth Registry (1945–1996) and/or Midwives Notification System (1980–1996) records. For each participant, data from the Hospital Morbidity Data Collection (HMDC, 1970–2014), the WA Cancer Registry (1982–2014), and the WA Death Registry (1969–2014), were provided by the WA Data Linkage Branch. All of these data are statutory collections and have complete WA population coverage over their retrospective time periods. Additionally, the Family Connections Project was used to determine and genealogically link all first-degree relatives (mother, father, siblings, and children) for each participant, using data from the Births, Deaths and Marriage Registries [15]. Linked health data (hospital, emergency department, cancer registry and mortality) were also provided for each relative.

Data from the WA Cancer Registry were used to identify all diagnoses of CRC in participants and their first-degree relatives. Data from the WA Death Registry were also used to identify individuals who died of CRC but were not included in the Cancer Registry (n = 16, 0.5% of all CRC diagnoses). ICD codes used to identify cases of CRC are include in Supplementary Table 1.

Demographic variables (year of birth and sex) were taken from the WA Birth Registry and/or Midwives Notification System records. Data from the HMDC, cancer and death registries were used to confirm year of birth and sex, with disparities resolved using the most common reported value. HMDC data were also used to identify comorbidities and risk factors associated with the development of CRC. These hospital data included principal diagnosis and up to 20 additional coded using International Classification of Disease (ICD), versions 8, 9 and 10 codes. The use of hospital data meant that only comorbidities identified in inpatient data were captured.

2.3. Risk factors

Candidate risk factors included age, sex, history of tobacco use (taken from hospital records) family history of CRC (first-degree relative) and procedure history (colonoscopy). Medical conditions that are known risk factors for CRC were also included (IBD, polyp, acute appendicitis and liver disease), as well as potential comorbidities/diseases associated with common risk factors (type 2 diabetes associated with obesity, alcohol related diagnoses) which had been diagnosed prior to CRC diagnoses. A history of non-CRC cancer was also examined.

Colonoscopy and polyps were combined into a single variable, given that colonoscopy is usually used to identify polyps, and were restricted to the 10 years prior to CRC diagnosis, death or the end of the study. Colonoscopies and the identification of polyps within 6 months of CRC diagnosis were excluded to account for delays in diagnosis. A 10-year lookback period was used as this is the maximum time generally recommended for subsequent colonoscopy [16,17]. Additionally, negative colonoscopy has been associated with a significant reduction in the incidence of distal CRC at 10 years following the procedure [18].

Each hospital record included the month and year of the admission, but not the time or day. As such, comorbidities were only included up to the month prior to diagnosis. Full details of the diagnosis and procedure codes use to identify CRC risk factors are included in Supplementary Table 1.

2.4. Data analysis

Univariable logistic regression models were initially used to examine associations between potential risk factors and CRC. A multivariable model was then created using stepwise backward elimination, including covariates with a p-value of less than 0.300 in the univariable analysis. Variable were retained in the multivariable model if they had a p-value less than 0.005. These analyses were conducted for the whole cohort, and then separately for each of the age-stratified groups of young (18–49 years) and middle-aged (50–69 years) individuals. Age was determined by age at CRC diagnosis for cases, and death or age at the 31st of December 2014 for non-diagnosed individuals. The relationship between age and CRC risk was further examined using joinpoint regression models in order to further investigate changes in the association between age and CRC.

All analyses was performed using StataMP, version 15 and Joinpoint Regression Program 4.4.0.0.

2.5. Ethics

The study was approved by the WA Department of Health Human Research Ethics Committee (2016/02) and reciprocal approval obtained from the University of Western Australia Human Research Ethics Committee (RA/4/1/8462).

3. Results

3.1. Demographics

The study cohort consisted of 1,030,836 individuals born in WA between 1945 and 1996. Of these, 11,422 (1.1%) people were excluded as they were diagnosed with CRC (n = 10) or died before the age of 18 years (n = 11,412), resulting in cohort of 1,019,414 individuals. The average age of participants was 40.4 ± 14.6 (mean ± standard deviation) years at the time of diagnosis, death or at the end of 2014, and 51.4% were male. A total of 3220 individuals were diagnosed with CRC prior to the end of December 2014 (0.32%). Of those diagnosed with CRC, 58.8% were male and the average age at diagnosis was 51.6 ± 10.0 years of age. The study included 713,085 individuals aged 18–49 years, including 1069 (0.15%) who had been diagnosed with CRC. A further 306,329 individuals were aged 50–69 years, with 2151 (0.70%) having been diagnosed with CRC. Within the whole study population, 2.7% had been hospitalized with a diagnosis of diabetes, 6.6% had been diagnosed with non-CRC cancer, and 9.8% had undergone a colonoscopy in the last 10 years.

3.2. First degree relatives

Within the study population, 50,539 (5.0%) individuals had a first-degree relative who had been previously diagnosed with CRC. Those aged 50–69 were more likely to have a first-degree relative with CRC

Table 1
Association between risk of colorectal cancer and having a first-degree relative previously diagnosed with colorectal cancer, stratified by age.

	All individuals (n = 1,019,414)				18 - 49 years (n = 713,085)				50 - 69 years (n = 306,329)			
	%[1]	OR	95% CI	P-value	%	OR	95% CI	P-value	%	OR	95% CI	P-value
Mother	1.9	2.52	2.14, 2.97	< 0.001	1.1	3.73	2.73, 5.11	< 0.001	3.9	1.32	1.09, 1.61	0.004
Father	2.5	1.90	1.61, 2.24	< 0.001	1.8	3.14	2.41, 4.11	< 0.001	4.3	1.01	0.82, 1.25	0.889
Sibling/s	0.7	3.18	2.50, 4.05	< 0.001	0.2	5.92	3.26, 10.75	< 0.001	1.8	1.45	1.12, 1.89	0.006
Child/ren	< 0.1	7.18	3.20, 16.15	< 0.001	< 0.1	- [2]	–	–	0.1	3.44	1.53, 7.74	0.003
Any first-degree	5.0	2.44	2.19, 2.72	< 0.001	2.9	3.60	2.95, 4.41	< 0.001	9.7	1.27	1.12, 1.45	< 0.001
One first-degree	4.8	2.44	2.18, 2.73	< 0.001	2.9	3.53	2.87, 4.33	< 0.001	9.2	1.30	1.14, 1.48	< 0.001
Two or more first degree	0.2	2.06	1.17, 3.64	0.131	0.1	6.19	2.31, 16.59	< 0.001	0.5	0.80	0.40, 1.61	0.535

OR = odds ratio; CI = confidence interval.
[1] Percentage of individuals that have a relative with CRC.
[2] Too few values for analysis.

(9.7%) compared to those aged 18–49 years (2.9%). In the univariable analysis, having a first degree relative was associated with an increased risk of CRC (Table 1). The odds ratio (OR) for the association between CRC and CRC in a first-degree relative was higher in young individuals compared with middle aged individuals.

3.3. Risk factors

In univariable analyses, the risk of CRC in the overall population was significantly higher in males and increased with increasing age (Table 2). However, when stratified by age, increasing age was associated with a significant reduction in CRC risk in middle-aged persons. Further investigation of age using joinpoint regression showed a progressive 11.5% per year increase in CRC risk until the age of 52 years. From 53 and 66 years of age the annual percent change was -0.3, however this was not significant. From age 67–69 years there was a significant decline of 46.8% percent per year.

In the whole cohort, a diagnosis of polyps in the previous 10 years was associated with an increased risk of CRC, with the largest risk in those diagnosed with polyps without a colonoscopy (although rare). This association remained consistent in young patients. However, in middle-age patients having a colonoscopy, regardless of the presence of polyps was associated with a reduction in the odds of CRC.

Smoking, diabetes, IBD, liver disease and non-CRC cancer diagnoses were all significantly associated with an increased odds of CRC (Table 1), with a larger effect size observed in younger individuals compared with middle-aged individuals. Patients with an alcohol-related diagnosis also had an increased risk of being diagnosed with CRC, however, the odds ratios were similar in young and middle-aged patients. Acute appendicitis was also associated with an increased risk of CRC overall but not when stratified by age.

3.4. Multivariable model

In the final multivariable model for the whole population, increasing age remained associated with a greater risk of CRC. However, as observed in the univariable analyses, when stratified by age this was only observed in young patients, while the reverse was seen in middle-aged patients (Table 3). Males had a higher risk of CRC overall and when stratified by age. Having a mother, father, sibling or child diagnosed with CRC was associated with an increased risk of CRC diagnosis in the multivariable model containing individuals of all ages. This was also true for young and middle-aged patients, with the exception of children in young individuals, and fathers in middle-aged individuals which were not associated with CRC.

A 10-year history of colonoscopy was associated with a reduced risk of CRC in the whole cohort, regardless of the presence or absence of polyps. The association between colonoscopy/polyps and CRC was marginally difference in the two age groups. In young patients only the absence of polyps as confirmed by colonoscopy was associated with a decreased risk of CRC (OR: 0.38, 95%CI: 0.26–0.54, p < 0.001). While in middle-age patients, having a colonoscopy in the previous 10 years

Table 2
Univariable analysis of risk factors associated with the diagnosis of CRC, stratified by age.

	All individuals (n = 1,019,414)				18 - 49 years (n = 713,085)				50 - 69 years (n = 306,329)			
	%[1]	OR	95% CI	P-value	%	OR	95% CI	P-value	%	OR	95% CI	P-value
Sex (reference: male)	51.4	0.74	0.69, 0.79	< 0.001	51.5	0.88	0.78, 1.00	0.042	51.0	0.67	0.61, 0.73	< 0.001
Age (years)	–	1.06	1.06, 1.06	< 0.001	–	1.12	1.11, 1.13	< 0.001	–	0.98	0.97, 0.99	< 0.001
History of tobacco use	10.9	3.76	3.49, 4.05	< 0.001	8.1	3.12	2.69, 3.61	< 0.001	17.3	2.73	2.50, 2.99	< 0.001
Comorbidities and disease history[2]												
Ten year history of polyps or colonoscopy[3]												
- No polyps/No CS	90.2		Base		95.0		Base		78.9		Base	
- Polyps/No CS	< 0.1	16.92	11.00, 26.01	< 0.001	< 0.1	35.21	18.59, 66.67	< 0.001	0.1	6.97	3.89, 12.49	< 0.001
- No polyp/CS	5.0	0.72	0.60, 0.87	0.001	3.4	1.04	0.75, 1.45	0.809	8.8	0.37	0.30, 0.46	< 0.001
- Polyps/CS	4.8	1.34	1.16, 1.54	< 0.001	1.6	2.88	2.15, 3.85	< 0.001	12.2	0.53	0.45, 0.63	< 0.001
IBD	0.7	3.71	2.95, 4.65	< 0.001	0.6	7.49	5.51, 10.18	< 0.001	0.9	1.79	1.27, 2.51	0.001
Appendicitis (acute)	0.3	1.79	1.09, 2.92	0.021	0.3	1.71	0.71, 4.12	0.233	0.3	1.77	0.97, 3.21	0.061
Diabetes	2.7	3.25	2.86, 3.69	< 0.001	1.3	2.72	1.97, 3.76	< 0.001	5.8	1.90	1.66, 2.19	< 0.001
Alcohol related admission	1.4	2.05	1.66, 2.52	< 0.001	1.2	2.02	1.37, 2.98	< 0.001	1.9	1.65	1.29, 2.11	< 0.001
Liver disease	0.8	3.65	2.95, 4.52	< 0.001	0.5	4.76	3.17, 7.14	< 0.001	1.4	2.12	1.65, 2.72	< 0.001
Non-CRC Cancer	6.6	2.68	2.44, 2.94	< 0.001	3.3	3.29	2.70, 4.02	< 0.001	14.4	1.38	1.24 – 1.54	< 0.001

CI = confidence interval, CS = colonoscopy, OR = odds ratio.
[1] Percentage of individuals in the cohort and the variable of interest.
[2] Prior to CRC diagnosis, identified in hospital records.
[3] Polyps in the colon or rectum (neoplastic or hyperplastic).

Table 3
Multivariable model for risk factors affecting the development of CRC in individuals, with separate models created for each age stratification. This multivariable model was the result of a stepwise backward elimination, using a significant p-value of 0.05.

	All individuals (n = 1,019,414)			18 - 49 years (n = 713,085)			50 - 69 years (n = 306,329)		
	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Sex	0.77	0.72, 0.83	< 0.001	0.84	0.75, 0.95	0.005	0.74	0.68, 0.81	< 0.001
Age	1.06	1.05, 1.06	< 0.001	1.11	1.10, 1.12	< 0.001	0.98	0.97, 0.99	< 0.001
History of tobacco use	2.86	2.63, 3.12	< 0.001	2.02	1.73, 2.35	< 0.001	3.08	2.78, 3.40	< 0.001
Mother	1.65	1.40, 1.95	< 0.001	2.21	1.61, 3.03	< 0.001	1.45	1.19, 1.76	< 0.001
Father	1.47	1.25, 1.74	< 0.001	1.94	1.48, 2.55	< 0.001	–	–	–
Sibling/s	1.60	1.26, 2.05	< 0.001	2.62	1.43, 4.80	0.002	1.53	1.17, 2.00	0.002
Child/ren	2.95	1.30, 6.68	0.010	–	–	–	3.68	1.62, 8.35	0.002
Ten year history of polyps and colonoscopy									
- Polyps and no CS	6.04	3.87, 9.42	< 0.001	12.92	6.61, 25.23	< 0.001	3.88	2.15, 7.02	< 0.001
- No polyps and CS	0.30	0.24, 0.36	< 0.001	0.38	0.26, 0.54	< 0.001	0.27	0.22, 0.34	< 0.001
- Polyps and CS	0.37	0.32, 0.43	< 0.001	0.81	0.59, 1.10	0.175	0.35	0.29, 0.41	< 0.001
IBD	3.92	3.09, 4.98	< 0.001	7.00	4.98, 9.82	< 0.001	2.28	1.61, 3.23	< 0.001
Diabetes	1.17	1.02, 1.34	0.025	–	–	–	1.25	1.08, 1.45	0.003
Alcohol	0.70	0.55, 0.87	0.002	–	–	–	0.65	0.50, 0.85	0.002
Liver disease	1.66	1.32, 2.09	< 0.001	1.76	1.16, 2.68	0.008	1.42	1.08, 1.86	0.011
Non-CRC cancer	1.19	1.08, 1.32	0.001	1.75	1.42, 2.15	< 0.001	1.15	1.03, 1.29	< 0.001

was associated with a reduced odds of CRC regardless of the detection of polyps. The detection of polyps without a colonoscopy was associated with a 13-fold increase in the risk of CRC in young patients, and an almost four-fold increase in middle-aged patients.

Diabetes, IBD, liver disease and non-CRC cancer were associated with an increased risk of CRC in the multivariable model, for the whole cohort and middle-aged patients. However, alcohol was associated with a reduced risk of CRC. In young patients, IBD, liver disease and non-CRC cancer were associated with an increased risk of CRC. With IBD in young patients in particular associated with a large increase in CRC compared with middle-aged patients.

4. Discussion

The risk factors associated with CRC in young and middle-aged individuals in WA were largely consistent, although the effect size varied for a number of risk factors between the two age groups. However, there were a number of notable exceptions.

Age was associated with an increased risk of CRC in patients up to the age of 52 years, with risk remaining relatively constant for patient aged 53–66 years and then subsequently declining. The reduction in CRC incidence after the age of 55, may be due increased investigation (e.g. colonoscopy) and early detection of polyps in this age group [19]. Overall and by age strata, the proportion of males diagnosed with CRC was significantly higher than females. The presence of higher rates of CRC in males is consistent with observations previously described in the literature for patients over 50 [20], however in young patients most studies have found no gender difference [21]. The definition of 'young' patients varies with some papers using < 40, or < 30 years old, compared with this study using < 50.

In fitting with the current literature, a history of tobacco use (or smoking) was associated with an increased risk of CRC in both young and middle-aged patients [22]. The identification of smoking in patients using hospital records has several limitations. Data is not available for patients who do not attend hospital and for patients who do attend hospital may under reported. The sensitivity and specificity of a history of smoking using hospital data has been reported at 45%–74% and 93%–97%, respectively [23]. Additionally, if it not possible to gauge the quantity or length of exposure.

The detection of polyps without a colonoscopy (i.e. via another method such as sigmoidoscopy, barium enema, CT scan and bowel resection) was associated with a large increase in the risk of CRC. However, the identification of polyps without a colonoscopy was relatively rare (< 0.1%). In middle-aged patients, a colonoscopy was associated with a reduction in the risk of CRC, regardless of the detection of polyps. Where as in young patients, while a 19% reduction in the CRC was observed in patients with polyps detected via a colonoscopy, this fell short of statistical significance perhaps due to the rare nature of this event in patients under 50 (1.6%).

Individuals with a first-degree relative who had been diagnosed with CRC were at an increased risk of being diagnosed with CRC. The association was largest in young patients, with the odds of CRC increased by 260% for individuals with one or more first degree relatives diagnosed with CRC compared with a 27% increase in middle-aged persons. In the multivariable model, having a child diagnosed with CRC was only associated with an increased risk of CRC in middle-aged patients, while having a father diagnosed with CRC was only associated with an increased risk of CRC in young-patients. Given the age of patients in the young strata and the average age of diagnosis of CRC, the likelihood of having a child with CRC was low.

A history of IBD was associated with an increased risk of CRC in both young and middle-aged persons. IBD has been previously associated with an increased risk of both polyps and CRC [24,25]. In young patients, the association between of IBD on CRC was more than double that of middle-aged patients (OR 7.00 compared with 2.28 in the multivariable model). CRC associated with IDB is known to affect patients at a younger age that sporadic CRC, with the average age of diagnosis 43.2 years in patients with IBD [26], while 90% of sporadic CRC occur in patients over 50 years of age [1].

Acute appendicitis was associated with a significantly increased risk of CRC in the univariate model, but not in the multivariable model or when stratified by age. Appendicitis resulting in appendicectomy has been proposed as both a potential risk factor and as a symptom of CRC [27–29]. In a Swedish study, an increased risk of CRC was observed following non-surgical treatment of appendicitis, with a standardized CRC incidence ratio of 39 (95%CI: 33–46) within the six months following appendicitis and 1.6 (95%CI: 1.3–1.9) after the initial six months [28]. Notably, in the Swedish study, cancer of the appendix was included in the definition of CRC, while the present study excluded it, due to the difference in pathology between cancer of the appendix and other cancers of the colon and rectum [30,31].

Consistent with previous studies, diabetes was associated with an increased risk of CRC [32]. This association may be explained by a combination of common risk factors (e.g. diet and body mass index), and the promotion of CRC via changes to the microenvironment caused by diabetes or the use of diabetes medications [32]. Of note, the inclusion of diabetes in this study relates to hospital admissions for diabetes rather than a diagnosis of diabetes. In our study, 2.7% of

participants had been admitted to hospital with a diagnosis or co-diagnosis related to diabetes, while the prevalence of diabetes in Australia is approximately 5.1% [33]. As such, it likely included patients with poorly managed diabetes or other comorbidities requiring hospitalization, which may have biased the results.

Admission to hospital with a liver disease related diagnosis was associated with an increased risk of CRC in the multivariable model in both age groups. The association between CRC and chronic liver disease has been previously identified and examined in a meta-analysis of 55,991 patients (50 studies), with a pooled standardized incidence rate ratio of 2.06 (95%CI: 1.46–2.90). It has been suggested that increased rates of CRC may occur in patients with liver disease due to immunological changes [34]. Both chronic and acute liver disease can reduce innate immune function [35], which has been shown to play an important role in the promotion of cancer [36].

Further, alcohol consumption is a common cause of liver disease and has also been associated independently with CRC diagnosis, with a systematic review of CRC in heavy drinkers compared with non/occasional drinkers reporting a risk ratio of 1.37 (95%CI: 1.26–1.49) [37]. In keeping with this, in the univariate model patients admitted to hospital with an alcohol related diagnosis were also more likely to be diagnosed with CRC. However, in the multivariable model alcohol was associated with 30% reduced risk of CRC. This is likely due to the relationship between heavy alcohol consumption and both liver damage and tobacco use (which were included in the multivariable model). It is unlikely that hospitalisations related to alcohol are protective, but are instead a result of other factors within the model. While data were not available on the levels of alcohol consumption of individuals in our study, it could be assumed that given their hospitalisation they had consumed alcohol at a risky level.

A prior diagnosis of other (i.e., non-CRC) cancer was associated with an increased risk of CRC in both young and middle-age persons. This risk may be attributed to individual susceptibility to cancer (e.g. Lynch syndrome), shared etiologic exposures (e.g. alcohol or diet) or as a result of cancer treatments. Both chemotherapy and radiation therapy used to treat cancer have been associated with an increased risk of subsequent cancer [38,39]. An increased risk of CRC has been identified in endometrial cancer survivors [40] and in patients with any cancer [41]. Unfortunately, data on treatment regimens were not available to further investigate the effects of cancer treatment. Similarly, due to the diverse range of cancers and their low prevalence in patients with CRC, the sample size was not sufficient to examine type specific primary cancers.

Recent trends in the increasing prevalence of CRC in young patients in Australia [42] may be in part driven by the increases in the prevalence of other diseases such as IBD [43] and liver disease [44]. Many of the diseases associated with CRC, also have common risk factors such as obesity and risky alcohol consumptions which are also increasing in Australia [45,46].

4.1. Clinical implications

The results suggest that a number of CRC risk factors that have been routinely used to identify high risk individuals in middle-aged and older populations may also be relevant in young patients. Interestingly, several of the risk factors that have been associated with increased risk of CRC in middle-aged patients had a stronger effect size in young patients. Individuals under the age of 50 years who fit this risk profile should be monitored more closely for CRC, to enable earlier detection and improve clinical outcomes.

4.2. Strengths and limitations

This study was able to utilize a large, naturalistic population and encompass family linkages across decades of health records. Whilst utilizing linked health data had a number of advantages in terms of being able to capture population-level data, there were also some limitations on the data that were available. For example, the study was only able to include comorbidities that are captured in hospital admission within WA from 1970 onwards. Comorbidities that were not severe enough to result in hospitalisation or resulted in a hospital admission outside of WA would not have been included. There are not currently ICD-10-AM codes for common genetic disorders associated with CRC, including Lynch and FAP, therefore we were unable to identify patients with these conditions. Similarly, the data would not have captured CRC diagnoses in interstate or overseas relatives, however these numbers would be expected to be low. Additionally data on a number of risk factors such as body mass index, physical activity, diet, and medication use which are known risk factors for CRC were not captured by the administrative data sources available for this study.

5. Conclusions

Risk factors associated with CRC diagnosis were generally consistent in young and middle-aged patients, however, many of the identified risk factors had a stronger association in young patients (e.g. IBD). Potentially there are a number of other risk factors that are specific to younger patients (genetic, hereditary, and environmental factors) that are yet to be identified or could not be examined using routine hospital data. Further investigation is required to help identify high risk young patients.

Author contribution

EM, PO, DP & SW conceived and designed the study.

SW applied for the data and obtained ethics for the study.

EK performed the analysis and drafted the manuscript with support from SW, GC and NM.

HE provided clinical context to the results and advised on clinical codes.

All authors reviewed the manuscript and approved the final version.

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Declaration of Competing Interest

The authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.101591.

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