RESEARCH ARTICLE

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Age-Specific Differences in the Risk of Colorectal Precursor Lesions Among Patients with Type 2 Diabetes Undergoing Surveillance Colonoscopy

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Abstract

Background: The incidence rate of colorectal cancer (CRC) in young adults is rising in parallel with type 2 diabetes (T2D). The majority of CRC develop through two main subtypes of precursor lesions; adenomas and serrated lesions. The associations between age and T2D on development of precursor lesions remain uncertain. **Objectives:** We studied the association of T2D with the development of adenomas and serrated lesions in individuals <50 versus ≥50 years of age, in a population undergoing long-term regular surveillance colonoscopy due to an elevated risk of CRC. **Methods:** A case-control study was conducted on patients who were enrolled in a surveillance colonoscopy program between 2010-2020. Findings at colonoscopy, clinical and demographic features were collected. Adjusted and unadjusted binary logistic regression assessed the association of age, T2D, sex, and other medical conditions and lifestyle-related factors with different subtypes of precursor lesions diagnosed at colonoscopy. Cox proportional hazards model analysis determined the association of T2D and other confounders with development time for precursor lesions. **Results:** Cases included 412 patients <50y [mean age 38.7 (range, 24-49y)] and 824 sex-matched controls ≥50y [62.1 (50-75y)]. Individuals <50y were less likely to have been diagnosed with T2D than those ≥50y (7% vs 22%, P-value<0.001). During the follow-up period, there was no significant association between T2D and diagnosis of any precursor lesions, but when considering development time, individuals with T2D developed non-significant adenomas earlier than those without T2D (HR =1.46; 95% CI: 1.14–1.87; P-value=0.003). However, this was not independent of age or findings at index colonoscopy. **Conclusions:** T2D does not further increase the incidence of adenomas or serrated lesions in either a young or older cohort undergoing long-term surveillance colonoscopy.

Keywords: Young-onset colorectal cancer- type 2 diabetes- screening- adenomas- serrated lesions- risk factors

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Introduction

Colorectal cancer (CRC) was the third most commonly diagnosed cancer and the second most common cause of cancer death globally in 2020 (Sung et al., 2021). While the overall incidence and mortality rate of CRC has been declining in recent years (American Cancer Society, 2021), both incidence and mortality of CRC in adults aged less than 50 years, referred to as young-onset CRC (YOCRC), have been rising worldwide (American Cancer Society, 2021; Mikaeel et al.,2019). The exact causes for the trend of rising CRC incidence rates in young adults are currently unknown.

Development of CRC can be prevented by removing precursor lesions (such as adenomas and serrated lesions) or if discovered in the early stages, can be treated by surgery alone without the need for chemotherapy or radiotherapy (Kanth and John, 2021). Screening programs using faecal occult blood tests and/or colonoscopy can detect cancers as well as advanced precursor lesions, which facilitates both prevention and early detection (Cole et al., 2013; Schreuders et al., 2015). However, most organised screening programs around the world recommend commencement of CRC screening at 50

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years of age, which neglects early detection of neoplasia in younger adults (Schreuders et al., 2015). Establishing the risk factors for neoplasia development in young individuals could allow for a more personalised screening approach.

While generational changes in diet, environmental exposures, and modern lifestyles (such as physical inactivity, obesity, and alcohol) are likely to be implicated in the observed rise in the incidence of YOCRC, no definitive risk factor has been identified (Muller et al., 2021). An individual's risk of CRC is mainly determined by age, a personal history of precursor lesions based on number and histological features of these, and whether there is a family history of CRC (Stoffel and Murphy, 2020). In the absence of family history, targeted screening and surveillance for people <50 years are only carried out in individuals with known predispositions to CRC such as inflammatory bowel disease (IBD) or evidence of pathogenic/likely pathogenic-germline variants. However, less than 10% of YOCRC cases are inherited in an autosomal-dominant manner, and 3 out of 4 cases of YOCRC have no family history of the disease (StoffelMurphy, 2020). Therefore, other potential risk factors need to be considered in this population.

Epidemiological studies suggest that there is an association between CRC and type 2 diabetes (T2D) (Gonzalez et al., 2017), with incidence rates of both diseases steadily rising in young adults (Joh et al., 2020; Khan et al., 2016; Mayer-Davis et al., 2017; Menke et al., 2015; Mikaeel et al., 2021; Xu et al., 2018). However, the findings of studies are not entirely consistent (Gonzalez et al., 2017) and this knowledge, thus, has not had a significant impact on clinical practice in the form of specific diagnostic tests or management approaches supported by clinical guidelines. The potential age and sex differences in the T2D population and their association with development of CRC remain uncertain. In older individuals, a systematic review showed that T2D was associated with a 27% higher risk of CRC (Tsilidis et al., 2015). However, in the younger cohort, there have been mixed findings (Chen et al., 2012; Elwing et al., 2006; Imperiale et al., 2008; Khan et al., 2020; La Vecchia et al., 1994; Vu et al., 2014). Longitudinal studies on the development of precursor lesions (such as adenomas and serrated lesions) in young adults and those diagnosed with T2D are lacking. Further exploration is needed to determine the association of T2D with the risk factors for developing YOCRC.

This study aimed to investigate the association of T2D and the development of precursor colorectal lesions in an elevated risk cohort undergoing regular surveillance colonoscopy. We assessed the incidence, development rate, and the types of polyps found in patients with and without T2D in individuals <50 and ≥50 years old.

Materials and Methods

Population

A case-control study was conducted on patients enrolled in the Southern Cooperative Program for the Prevention of Colorectal Cancer (SCOOP) program and who underwent colonoscopies for surveillance purposes. The SCOOP program is a South Australian-based program that coordinates surveillance colonoscopies for people at elevated risk of CRC at the Flinders Medical Centre (Bedford Park, South Australia), the Repatriation General Hospital (Daw Park, South Australia), and Noarlunga Hospital (Noarlunga Centre, South Australia) (Cancer Council Australia, 2019). Elevated risk was defined as individuals that had a finding of adenoma or serrated lesion at index colonoscopy, or those that had a significant family history of CRC (Bampton et al., 2002; Cancer Council Australia, 2018). Colonoscopy outcome data was extracted for people who underwent complete and good quality colonoscopies from January 2010 until September 2020. Colonoscopy procedure date, family history of CRC, pathology outcomes, and demographics (age and sex) were collected. Additional metrics including T2D, body mass index (BMI), current or previous medical conditions, medication usage, smoking, and drinking status were also collected from clinical records.

To assess age-specific associations on the risk of advanced neoplasia in patients with and without T2D, the included cohort were assigned as individuals aged <50 years ("cases") or ≥50 years ("controls") at their index colonoscopy and had at least one follow-up surveillance colonoscopy. Controls were randomly selected (with a random number generator) at the rate of two per case and matched on sex. Exclusion criteria included patients with genetic risk factors for CRC, personal history of IBD, or diagnosed with CRC at the index procedure. Patients who underwent colonoscopies before 2010 were also excluded since serrated lesions were not adequately reported by endoscopists and were largely considered as benign hyperplastic polyps by pathologists before classification of these lesions were updated by the World Health Organization in 2010 (Crockett and Nagtegaal, 2019).

Significant polyps were defined as previously described (Molmenti et al., 2020). Any other adenomatous polyps or serrated lesions which did not meet these criteria were classified as non-significant adenomas/serrated lesions. Mixed significant polyps were classified as adenomas and serrated lesions with at least one of them meeting the criteria for significant polyps. Mixed non-significant polyps were classified as non-significant adenomas and non-significant serrated lesions.

Statistics

Prevalence of demographics and colonoscopy outcomes were compared between cases and controls using Pearson's chi-squared or Fisher's exact test as appropriate. Adjusted binary logistic models were performed to test for the association between the presence of different types of precursor lesions [significant and non-significant adenomatous polyps and serrated lesions (for the index colonoscopy)] versus diabetes, sex and age as a categorical variable. Multivariable binary logistic regressions were performed for the same outcomes by adding all a priori predictors in an initial adjusted model then using backwards elimination to remove the confounder with the highest P-value one at a time until all confounders had P-value <0.2 (Heinze and Dunkler,

2017), with results expressed as odds ratio (OR) with 95% confidence interval (CI) and comparison and global P values. Variables that have previously been suggested to be associated with neoplasia development (Bailie et al., 2017; Kim et al., 2016; Low et al., 2020; Rosato et al., 2013) were included in the initial adjusted models. Cox proportional hazards model analysis was performed for time to significant and non-significant adenomas, serrated lesions and CRC (for up to 5 surveillance colonoscopies following the index colonoscopy) versus diabetes, sex and binary age (described in detail in the Supplementary Data).

Results

A total of 1371 participants aged <50 years were enrolled into the surveillance program during the study period. Cases were excluded due to being >50 years on their second (first surveillance) colonoscopy (n=522) or having a medical history of IBD (n=202), CRC (n=132), or hereditary CRC syndromes (n=52). In addition, 26 patients who had incomplete index colonoscopies or poor bowel preparation, 12 patients who had no clinical reports, and 13 patients who had no follow-up colonoscopy were excluded. Finally, 412 cases [mean age 38.7 (range, 24-49 years)] met study eligibility criteria and were included in this study. We then randomly selected 824 controls [mean age 62.1 (range, 50-75 years)], matching for sex, and who had at least 2 colonoscopies in the same time period (Supplementary Figure 1).

Descriptive analysis of the study population and colonoscopy results

The characteristics of the patients are shown in Table 1. Compared to patients aged ≥50 years old, the younger cohort were more likely to have a first degree relative with CRC (P-value <0.001) and be a current smoker (P-value =0.04). Patients aged ≥50 years were more likely to have T2D (P-value <0.001), and personal history with another cancer (P-value <0.001), There were no significant differences between both age groups in terms of BMI status (P-value =0.41). Drinking status (P-value =0.50), depression and/or anxiety (P-value =0.65), appendectomy (P-value =0.53), and tonsillectomy (P-value =0.81).

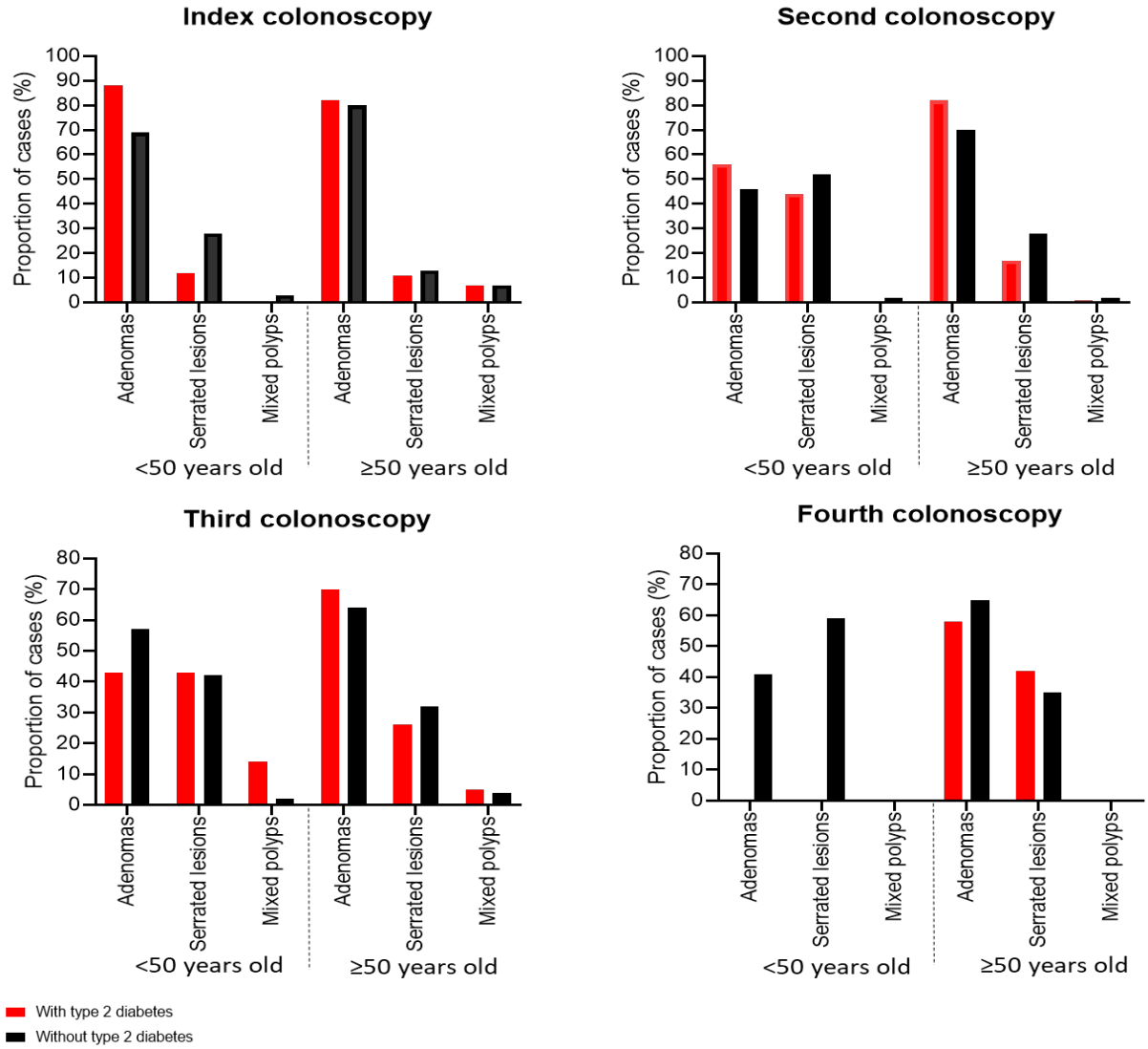

Figure 1. Association of Type 2 Diabetes with Precursor Lesions of Colorectal Cancer in Individuals <50 and ≥50 Years in the Index Colonoscopy, Second Colonoscopy, Third Colonoscopy, and Fourth Colonoscopy.

Table 1. Study Participant Details

Characteristics	<50 years (%)	≥50 years (%)	P value ‡
Total number of patients	412 (33.3)	824 (66.7)	
Mean (SD)	38.7 (8.3)	62.1 (6.7)	
Sex			1.000
Female	218 (52.9)	436 (52.9)	
Male	194 (47.1)	388 (47.1)	
First-degree relative with CRC			< 0.001
Yes	122 (29.6)	151 (18.3)	
No	290 (70.4)	673 (81.7)	
Personal history with other cancer [a,a*]			< 0.001
Yes	5 (1.5)	40 (6.6)	
No	331 (98.5)	562 (93.4)	
Type 2 Diabetes [b,b*]			< 0.001
Yes	23 (7.0)	133 (22.1)	
No	307 (93.0)	469 (77.9)	
BMI (kg/m^2) [c,c*]			0.414
<25	45 (23.9)	81 (19.2)	
25-30	61 (32.4)	145 (34.4)	
>30	82 (43.6)	196 (46.4)	
Smoking [d,d*]			0.039
Never smoked	63 (35.4)	117 (34.9)	
Current smoker	67 (37.6)	95 (28.4)	
Ex-smoker	48 (27.0)	123 (36.7)	
Drinking alcohol [e,e*]			0.502
>10 glasses/week	18 (15.1)	27 (12.2)	
≤ 10 glasses/week	101 (84.9)	195 (87.8)	
Depression and or anxiety [f,f*]			0.650
Yes	59 (17.6)	99 (16.4)	
No	276 (82.4)	503 (83.6)	
Appendicectomy [g,g*]			0.531
Yes	24 (7.2)	51 (8.5)	
No	311 (92.8)	549 (91.5)	
Tonsillectomy [h,h*]			0.814
Yes	10 (2.9)	22 (3.7)	
No	330 (97.1)	580 (96.3)	
Hypertension and/or high cholesterol [i,i*]			< 0.001
Yes	73 (21.8)	350 (58.1)	
No	262 (78.2)	252 (41.9)	
On anti-inflammatory medications [j,j*]			< 0.001
Yes	9 (2.9)	93 (15.8)	
No	297 (97.1)	495 (84.2)	
Taking Vitamin D and/or Calcium [k,k*]			0.041
Yes	17 (5.6)	58 (9.6)	
No	289 (94.4)	544 (90.4)	

BMI, body mass index; CRC, colorectal cancer; SD, standard deviation; number of patients <50 years with missing data for: a = 76, b = 82, c = 224, d = 234, e = 293, f = 77, g = 77, h = 72, i = 77, j = 106, k = 106; number of patients ≥50 years with missing data for: a* = 222, b* = 222, c* = 402, d* = 489, e* = 602, f* = 222, g* = 224, h* = 222, i* = 222, j* = 236, k* = 222. ‡: Pearson's chi-squared test or Fisher's exact test P-value as appropriate.

Table 2. Pathology Findings at Each Colonoscopy

Outcome	<50 years (%)	≥50 years (%)	P value‡
Index colonoscopy			
Non-significant polyps	196 (47.6)	443 (54.2)	< 0.001
Significant polyps	121 (29.4)	292 (35.7)	
Normal	95 (23.1)	82 (10.0)	
Non-significant adenoma	133 (42.2)	368 (50.4)	< 0.001
Significant adenoma	86 (27.3)	226 (31.0)	
Significant serrated lesions	29 (9.2)	19 (2.6)	
Non-significant serrated lesions	59 (18.7)	71 (9.7)	
Significant mixed	6 (1.9)	45 (6.2)	
Non-significant mixed	2 (0.6)	1 (0.1)	
Second colonoscopy			
Mean time since index colonoscopy (SD)	3.0 years (2.1)		
Non-significant polyps	177 (43.0)	429 (52.4)	0.004
Significant polyps	54 (13.1)	97 (11.8)	
Tumour	1 (0.2)	8 (1.0)	
Normal	180 (43.7)	285 (34.8)	
Non-significant adenoma	81 (35.4)	314 (59.6)	< 0.001
Significant adenoma	27 (11.8)	70 (13.3)	
Significant serrated lesions	24 (10.5)	18 (3.4)	
Non-significant serrated lesions	94 (41.0)	116 (22.0)	
Significant mixed	3 (1.3)	9 (1.7)	
Non-significant mixed	0 (0.0)	0 (0.0)	
Third colonoscopy			
Mean time since the second colonoscopy (SD)	2.6 years (1.9)		
Non-significant polyps	64 (41.8)	160 (51.3)	0.030
Significant polyps	16 (10.5)	45 (14.4)	
Tumour	1 (0.7)	1 (0.3)	
Normal	72 (47.1)	106 (34.0)	
Non-significant adenoma	33 (40.2)	108 (52.7)	0.027
Significant adenoma	8 (9.8)	24 (11.7)	
Significant serrated lesions	8 (9.8)	10 (4.9)	
Non-significant serrated lesions	31 (37.8)	52 (25.4)	
Significant mixed	1 (1.2)	11 (5.4)	
Non-significant mixed	1 (1.2)	0 (0.0)	
Fourth colonoscopy			
Mean time since the third colonoscopy (SD)	2.0 years (1.5)		
Non-significant polyps	29 (56.9)	51 (54.8)	0.540
Significant polyps	5 (9.8)	15 (16.1)	
Tumour	0 (0.0)	0 (0.0)	
Normal	17 (33.3)	27 (29.0)	
Non-significant adenoma	12 (35.3)	32 (50.0)	0.130
Significant adenoma	3 (8.8)	11 (17.2)	
Significant serrated lesions	2 (5.9)	4 (6.3)	
Non-significant serrated lesions	17 (50.0)	17 (26.6)	
Significant mixed	0 (0.0)	0 (0.0)	
Non-significant mixed	0 (0.0)	0 (0.0)	

Significant adenomas, tubular adenoma ≥1 cm or any adenoma with villous features or high-grade dysplasia regardless of the size; significant serrated lesions, sessile serrated lesion (SSL) ≥1 cm or SSL with cytological dysplasia, or traditional serrated adenoma of any size; non-significant adenomas/serrated lesions, polyps that did not meet the criteria of significant polyps. Significant mixed: adenomas and serrated lesions with at least one of them being significant; non-significant mixed, non-significant adenomas and non-significant serrated lesions. ‡, Pearson's chi-squared test or Fisher's exact test P-value as appropriate.

Table 3. Unadjusted and Adjusted Binary Logistic Regressions for Precursor Lesions Diagnosed at the Index Colonoscopy: adenoma and serrated versus diabetes, sex, age (binary), and confounders.

Adjustment	Outcome	Predictor/Confounder	Comparison	Odds Ratio* (95% CI)	Global P value
Unadjusted	Non significant Adenoma	Age_50y	≥50 vs <50	1.62 (1.21, 2.17)	0.001
		Sex	Male vs Female	1.09 (0.84, 1.43)	0.511
		Diabetes	Yes vs No	1.08 (0.75, 1.54)	0.684
Adjusted	Non significant Adenoma	Age_50y	≥50 vs <50	2.08 (1.21, 3.58)	0.008
		Alcohol consumption	>10 drinks vs ≤10 drinks**	0.37 (0.16, 0.85)	0.020
		Anti-inflammatories	Yes vs No	0.50 (0.19, 1.30)	0.154
		Depression/Anxiety	Yes vs No	0.57 (0.30, 1.06)	0.076
		Sex	Male vs Female	1.18 (0.72, 1.93)	0.510
		Diabetes	No vs Yes	0.84 (0.44, 1.60)	0.590
Unadjusted	Significant Adenoma	Age_50y	≥50 vs <50	1.55 (1.12, 2.14)	0.008
		Sex	Male vs Female	1.92 (1.43, 2.59)	<0.001
		Diabetes	Yes vs No	1.01 (0.69, 1.50)	0.948
Adjusted	Significant Adenoma	Age_50y	≥50 vs <50	2.06 (1.11, 3.85)	0.023
		Alcohol	>10 drinks vs ≤10 drinks**	1.72 (0.80, 3.69)	0.162
		Depression/Anxiety	Yes vs No	1.92 (1.03, 3.56)	0.039
		FDR with CRC	Yes vs No/Unknown	0.51 (0.25, 1.04)	0.065
		Sex	Male vs Female	2.68 (1.56, 4.61)	<0.001
		Diabetes	Yes vs No	1.20 (0.62, 2.31)	0.591
Unadjusted	Non significant. Serrated Lesions	Age_50y	≥50 vs <50	0.57 (0.37, 0.88)	0.012
		Sex	Male vs Female	0.37 (0.23, 0.60)	<0.001
		Diabetes	Yes vs No	0.87 (0.45, 1.66)	0.670
Adjusted	Non significant Serrated Lesions	Age_50y	≥50 vs <50	0.35 (0.16, 0.75)	0.008
		Alcohol	>10 drinks vs ≤10 drinks**	3.85 (1.47, 10.08)	0.006
		Anti-inflammatories	Yes vs No	4.10 (1.08, 15.53)	0.038
		Sex	Male vs Female	0.20 (0.08, 0.51)	0.001
		Diabetes	Yes vs No	0.44 (0.12, 1.65)	0.224
Unadjusted	Significant Serrated Lesions	Age_50y	≥50 vs <50	0.42 (0.21, 0.85)	0.015
		Sex	Male vs Female	0.31 (0.14, 0.70)	0.005
		Diabetes	Yes vs No	0.66 (0.19, 2.26)	0.511
Adjusted	Significant Serrated Lesions	Age_50y	≥50 vs <50	0.66 (0.23, 1.94)	0.452
		Sex	Male vs Female	0.23 (0.06, 0.84)	0.026
		Diabetes	Yes vs No	0.77 (0.09, 6.35)	0.810
		Depression/anxiety	Yes vs No	0.21 (0.03, 1.67)	0.141
		Smoking status	Yes vs No/Ex	3.95 (1.33, 11.72)	0.013

*Modelling the probability that non-significant/significant adenomas/serrated lesions = "Yes"; **Number of alcoholic drinks per week. CRC, Colorectal cancer; FDR, First-degree relative.

Table 2 shows the outcome of each colonoscopy. Approximately 86% (1052/1229) of study participants were diagnosed with precursor lesions at the index colonoscopy. Of these, 61% (639/1052) had non-significant polyps and 39% (413/1052) had significant polyps. The mean interval between index colonoscopy and the second examination was 3.0 years (SD =2.1 years). At the second colonoscopy, 0.7% (9/1231) of patients were diagnosed with colorectal tumours [one patient was without T2D and aged <50 years, and 8 cases were aged ≥50 years (4/6 of these with known diabetes status had T2D)]. Patients with T2D were at significantly higher risk of developing CRC (2.6%, 4/156) at the second colonoscopy compared to those without T2D [0.4%, 3/776, P-value =0.02). There was a lower overall proportion of significant precursor lesions found at the second colonoscopy, with diagnosis rates at approximately 12% of the cohort, with patients aged <50 years were less likely to be diagnosed with any precursor lesions compared to the older cohort (P-value <0.004). Incidence of significant and non-significant serrated lesions was higher among patients aged <50 years compared to those aged ≥50 years (P-value <0.001). However, adenomas were more likely to be detected among patients ≥50 years (P-value <0.001). The overall findings of the subsequent colonoscopies were comparable to the index and first surveillance colonoscopies (Table 2).

Table 4. Cox Proportional Hazard Models of Time to Non-Significant and Significant Adenoma and Serrated Lesions versus Diabetes

Adjustment	Outcome	Predictor/Confounder	Comparison	Hazard Ratio (95% CI)	Comparison P-value	Global P-value
Sex-adjusted	Time to non-sig adenoma	Diabetes	Yes versus No	1.46 (1.14, 1.87)		0.003
		Sex	Male vs Female	1.33 (1.09, 1.64)		0.006
Adjusted	Time to non-significant adenoma	Diabetes	Yes versus No	1.25 (0.97, 1.60)		0.086
		Age – binary	≥50 vs <50	1.85 (1.45, 2.36)		<0.001
		Sex	Male vs Female	1.29 (1.05,1.59)		0.015
		Index colonoscopy finding	Serrated lesions vs adenomas	0.96 (0.72, 1.28)	0.789	0.041
			Other vs adenomas	0.66 (0.48, 0.91)	0.012	
Sex-adjusted	Time to non-significant serrated lesions	Diabetes	Yes versus No	0.85 (0.58, 1.24)		0.401
		Sex	Male vs Female	0.85 (0.65, 1.10)		0.219
Adjusted	Time to non-sig serrated lesions	Diabetes	Yes versus No	0.67 (0.51, 0.88)		0.774
		Age – binary	≥50 vs <50	0.67 (0.51, 0.88)		0.004
		Sex	Male vs Female	0.90 (0.69, 1.17)		0.421
		Index colonoscopy finding	Adenomas vs Serrated lesions	0.41 (0.30, 0.54)	<0.001	<0.001
			Other vs Serrated lesions	0.21 (0.13, 0.33)	<0.001	
Sex-adjusted	Time to significant adenoma	Diabetes	Yes versus No	1.34 (0.84, 2.13)		0.216
		Sex	Male vs Female	1.24 (0.85, 1.82)		0.263
Adjusted	Time to significant adenoma	Diabetes	Yes versus No	1.21 (0.76, 1.95)		0.423
		Age – binary	≥50 vs <50	1.30 (0.83, 2.01)		0.249
		Sex	Male vs Female	1.10 (0.75, 1.61)		0.632
		Index colonoscopy finding	Serrated lesions vs adenomas	0.43 (0.22, 0.83)	0.011	0.002
			Other vs adenomas	0.37 (0.19, 0.75)	0.006	
Sex-adjusted	Time to significant serrated lesions	Diabetes	Yes versus No	0.68 (0.29, 1.61)		0.379
		Sex	Male vs Female	0.73 (0.41, 1.30)		0.282
Adjusted	Time to significant serrated lesions	Diabetes	Yes versus No	0.80 (0.33, 1.93)		0.623
		Age – binary	≥50 vs <50	0.68 (0.38, 1.21)		0.192
		Sex	Male vs Female	0.89 (0.48, 1.54)		0.601
		Index colonoscopy finding	Adenomas vs Serrated lesions	0.23 (0.13, 0.42)	<0.001	<0.001
			Other vs Serrated lesions	0.13 (0.04, 0.37)	<0.001	

Type 2 diabetes and the risk of adenomas and serrated lesions

At the index colonoscopy there were no statistically significant associations between T2D and other clinical variables with a finding of any significant or non-significant adenomas or serrated lesions. However, the male sex and older age were independently associated with the risk of finding significant adenomas, and smoking and female sex were significantly associated with the risk of significant serrated lesions at the index colonoscopy (Table 3). Patients aged ≥50 years were 2.06 times at higher risk of developing significant adenomas compared to the younger group in the adjusted model (Table 3; OR= 2.06, 95% CI:1.11-3.85, P-value = 0.023).

When colonoscopy findings throughout surveillance were considered, there was a trend observed for a higher incidence of adenomas at the index and first surveillance colonoscopies (second colonoscopy) for individuals <50 years with T2D (Figure 1), but overall, there were no significant differences found between precursor lesion types when considering the age groups separately and comparing those with and without T2D (Supplementary Table 1).

Type 2 diabetes and the time to develop adenomas and serrated lesions

Patients with T2D developed non-significant adenomas faster after the index colonoscopy than those without T2D (Figure 2A; HR=1.46, 95% CI: 1.14-1.87, P-value =0.002). However, this association did not hold true for time to development of significant adenomas, significant or non-significant serrated lesions (Figure 2B-D). When age and the index colonoscopy finding were considered in the adjusted model, T2D was not significantly associated with a finding of any of the precursor types (Table 4). There was also a significant association between T2D and time to CRC development (Supplementary figure 2 and Supplementary Table 2; HR=4.12, 95% CI: 1.10-15.45, P-value =0.036). However, this association was not significant in an adjusted model with age and sex (P-value = 0.067) or with age, Sex, and index colonoscopy finding (P-value = 0.071).

There was a significant association between the development of non-significant adenomas or serrated lesions and age, independent of T2D status. Findings of adenomas and serrated lesions at the index colonoscopy were significantly associated with time to development

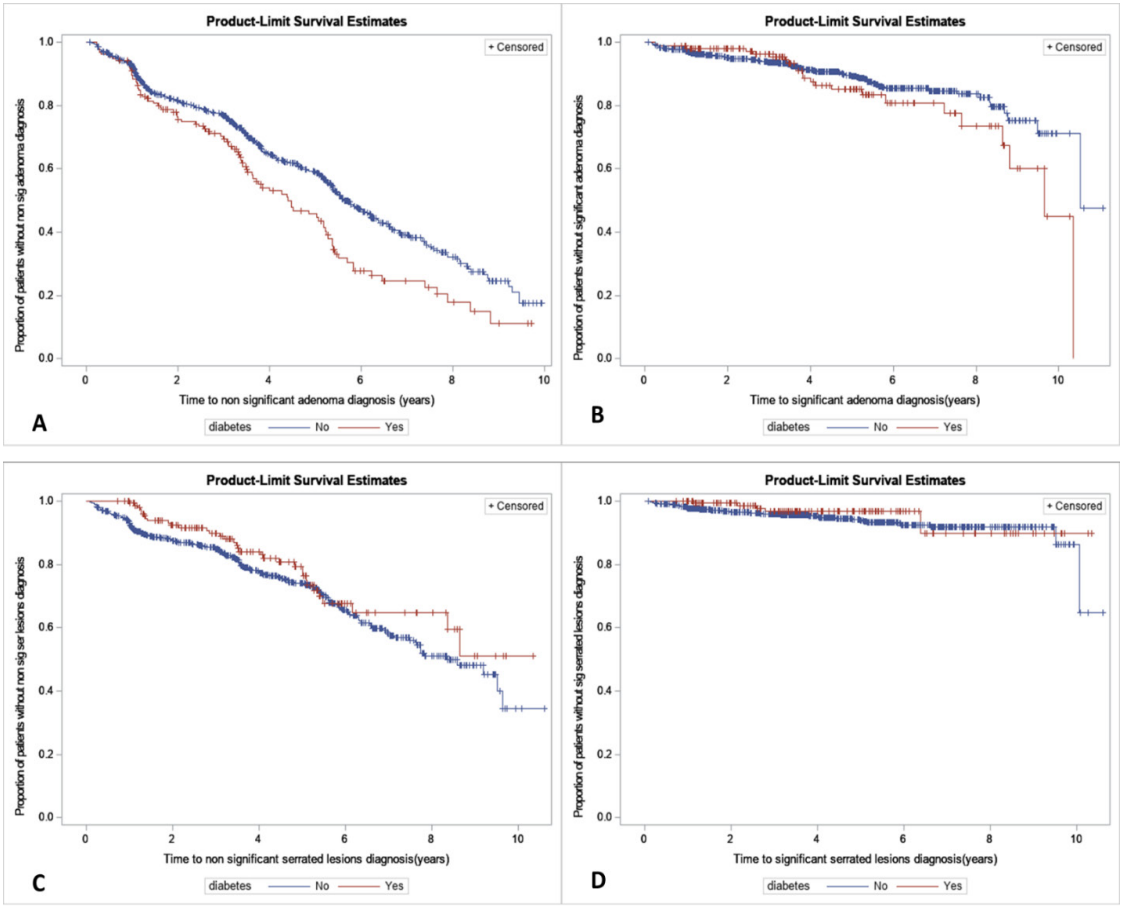

Figure 2. Kaplan-Meier Curves for Time Measured from the Index Colonoscopy to Polyp Detection during Surveillance versus Type 2 Diabetes (Yes/No). A, Time to non-significant adenomatous polyps; B, Time to significant adenomatous polyps; C, Time to non-significant serrated lesions; D, Time to significant serrated lesions.

of adenomas and serrated lesions, respectively (Table 4).

Discussion

Among YOCRCs and in the general population, the adenoma-carcinoma pathway contributes to the development of approximately 85% of all CRCs, with the alternative serrated neoplasia pathway accounting for up to 20% of CRCs (Pai et al., 2019). Previous studies are inconsistent regarding the association of non-hereditary factors with the risk of CRC or of the precursor lesions in young adults (SiegelJakubowski et al., 2020; Siegel et al., 2019). In this case-control study, we found that T2D was not independently associated with time for development of neoplasia in individuals undergoing regular surveillance colonoscopy, but patients with T2D were approximately 7-times more likely to develop CRC compared to patients without this condition.

There is conflicting evidence in the current literature as to whether T2D in young adults increases the risk of precursor lesions or CRC. In agreement with the lack of association between T2D and incidence of adenomas, a number of other reports showed no significant association between T2D and precursor lesions of CRC (Budzynska et al., 2018; Colussi et al., 2018; Dash et al., 2014; Hsu et al., 2021; Joh et al., 2020). Budzynka et al., (2018) conducted a retrospective study and observed no significant association between T2D and adenomas after adjusting for other confounders (such as sex, age, race/ethnicity, and BMI) (Budzynska et al., 2018). Similar findings were observed in a nationwide population-based study in Taiwan that showed no significant difference in the risk of developing CRC precursor lesions in patients with and without T2D (Hsu et al., 2021). In contrast, Vu et al. reported that diabetic patients aged 40-49 years were at higher risk of developing any type of colorectal adenomas than the non-diabetic cohort after adjusting for BMI, smoking, alcohol, and ethnicity (OR = 3.1; 95% CI: 1.5-6.4), but the study did not find a significant association between diabetes and the risk of developing significant colorectal adenomas (OR = 1.4; 95% CI: 0.6-3.4) (Vu et al., 2014). More recently, Ottaviano et al. reported a significant association between adenoma detection rate and T2D in the multivariable analysis (OR = 1.49; 95% CI: 1.13–1.97), and this link was higher in those who were not on diabetes medications (OR = 2.38; 95% CI: 1.09–5.2) (Ottaviano et al., 2020). However, neither study investigated the association of T2D with the risk of colorectal polyps in patients under 50 years old. These findings suggest that further research is needed to investigate the role of T2D in developing adenomas in young adults. Consistent with the findings of other studies (Budzynska et al., 2018; Colussi et al., 2018; Ottaviano et al., 2020), we have shown a significant association

between older age, male sex, drinking and depression/anxiety with the risk of developing colorectal adenomas. Male sex and increased age were also associated with the time to develop non-significant adenomas.

It is difficult to reconcile the apparent dichotomy of an increased risk for YOCRC but not for the precursor adenoma in T2D patients, given the clear evidence for the precursor lesion/cancer sequence. Cross-sectional studies such as the current study cannot take into account a possible metabolic effect of disturbed homeostatic conditions in diabetes and how they might influence dwell time (time within a stage) and transition rates (rate of movement from one stage to the next) (Gonzalez et al., 2017). For instance, one explanation for the dichotomy is that dwell time is not affected but transition to an invasive lesion (cancer) is, with our study showing a higher proportion of CRC found at surveillance colonoscopy in patients with T2D compared to those without diabetes, although it is worth noting that the sample size with this outcome was small. More studies are needed to better understand how the homeostatic disturbances in diabetes might influence the process of colorectal oncogenesis.

Reasons for the discordant findings regarding the risk of CRC and its precursor lesions in young adults could be related to the differences in the study cohort size, type of diabetes, duration of diabetes and follow up time, medications (such as metformin, insulin therapy, and anti-inflammatory drugs), the difference in the primary colonoscopy outcome (CRC or colorectal polyps) or most importantly study participants and control of potential confounders. For example, several studies (Ottaviano et al., 2020; Suh et al., 2011) that have shown a significant association between diabetes and the risk of precursor lesions did not have data regarding diet, physical activity, smoking, or other lifestyle-related risk factors. When these factors were adjusted by other studies (Budzynska et al., 2018; Hsu et al., 2021), the significant association did not persist. Some patients might have been diagnosed with T2D after the index colonoscopy and therefore, the follow-up time in our study might not have been sufficient to observe the significant association between T2D and development of adenomas and serrated lesions. In addition, various medications have been reported to be associated with increasing (Palmqvist et al., 2002; Sandhu et al., 2002) or decreasing (Cole et al., 2009; HigurashiNakajima, 2018; Umezawa et al., 2019) the risk of CRC. For example, metformin and nonsteroidal anti-inflammatory drugs, including aspirin, have been reported to have a preventive effect on colorectal carcinogenesis (Cole et al., 2009; Higurashi and Nakajima, 2018; Umezawa et al., 2019). Therefore, all of these factors should be considered when investigating the role of T2D in developing CRC and colorectal polyps in in future.

CRC screening in average-risk individuals begins at age 45 years in the US (Davidson et al., 2021). However, a significant number of YOCRC occurs among people aged <45 years (Siegel et al., 2020) and data from 1974-2013 demonstrate that the increase in the incidence of YOCRC is highest among the very youngest individuals (20-29 years old) (Siegel et al., 2017). Therefore, lowering the recommended age to 45 years to initiate screening is only one step in addressing YOCRC. Clearly, there is an urgent need to identify young adults who are at higher risk of developing YOCRC so that prevention strategies can be targeted and implemented earlier for a more personalized approach to CRC screening. Recently, a study reported that if diabetes is diagnosed <50 years old, CRC occurs at earlier ages (median: 59 years) compared to the general population (median: 71 years) (Khan et al., 2020). While the significant association between T2D and the time of developing adenomas or serrated lesions did not persist in the adjusted model within our study, our findings suggest that diabetic patients might develop CRC earlier than the non-diabetic group, which may increase in incidence if regular surveillance colonoscopy does not occur.

This study has number of strengths including its long term and complete follow up, the entire cohort had at least two colonoscopies, high-risk individuals (such as those with genetic risk factors or IBD) were excluded, and data related to important possible confounders (smoking, BMI, and drinking) were available. However, we also acknowledge several limitations. First, the study participants were enrolled in a long-term surveillance colonoscopy due to an elevated risk for the development of CRC. Therefore, the results of this study may not be applicable to the general population. Second, the small number of young patients with T2D included in this study. Third, as a retrospective cohort study, the study was limited to data found in clinical records. Fourth, metformin treatment status not being included in the final analysis. Observations suggest that the prodromal stages of T2D where insulin is particularly high may initiate neoplasia, and hence treatment to control glucose levels may remove the stimulus for further lesions to progress (Gonzalez et al., 2017). In addition, T2D and other confounders (such as drinking and smoking) were self-reported, and many cases of T2D may not have been diagnosed yet. Finally, data related to other possible confounders such as unhealthy diet and lack of physical activity were not available.

In conclusion, adjusting for age, we found no significant association between T2D and significant or non-significant adenomatous polyps or serrated lesions in individuals under surveillance colonoscopy, but despite limited numbers, an increased risk for CRC during surveillance was observed in individuals with T2D. In light of these early findings, further prospective studies of the general population are needed to fully understand whether a diagnosis of T2D at a young age may trigger entry to a CRC surveillance program. However, the development of CRC in T2D patients under surveillance points to the necessity of monitoring those exhibiting precursor lesions to remain in surveillance programs.

Author Contribution Statement

Reger R. Mikaeel: writing original draft, data collection, data analysis and interpretation, study design and concept. Suzanne Edwards: statistical analysis and data interpretation, writing, review, and editing. Jean Winter: study design and concept, data interpretation,

writing, review, and editing. Joanne P. Young and Graeme P Young: study design and concept, writing, review and editing. Timothy J. Price: supervision, study design and concept, writing, review and editing. Erin L. Symonds: supervision, study design and concept, data collection and interpretation, writing, review and editing.

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Ethics approval statement

This study was approved by the Southern Adelaide Clinical Human Research Ethics Committee (EC00188).

Conflict of interests

All authors declare that there is no conflict of interest.

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