

Different factors are associated with conventional adenoma and serrated colorectal neoplasia

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ABSTRACT

Current data shows there are differences in factors associated with colorectal neoplasia based on geographical location and cultural settings. There are no studies focusing on the association between environmental factors and colorectal polyps in Australia. The aim of this study was to prospectively evaluate the association of various factors with different colorectal neoplasia histology. We utilized a simplified one-page questionnaire for patients undergoing colonoscopy for information on age; gender; comorbidities; family history of colorectal cancer; physical activity; smoking; diet; alcohol intake; and body mass index. Factors were then evaluated for association with the presence of: (1) neoplastic lesions; (2) conventional adenomas; (3) neoplastic serrated polyps; (4) any lesions (past and present); and (5) hyperplastic polyps. 291 procedures and 260 patients were included. Factors with a p-value <0.2 in a univariate regression were included in an initial multivariable regression model. Backwards elimination was then performed, removing one predictor at a time until only significant predictors remained. In the final multivariable model, age \geq 65, male gender, type-2 diabetes mellitus, active smoking and family history of colorectal cancer were found to be statistically significant predictors for the presence of colorectal neoplasia. However, the significant predictors found for conventional adenomas (older age, male gender and smoking) were different from the significant predictors for neoplastic serrated polyps (type-2 diabetes mellitus and family history of colorectal cancer). Older age, male gender, type-2 diabetes mellitus, and smoking were significantly associated with the presence of colorectal neoplasia. The factors associated with conventional adenomas differed from those associated with neoplastic serrated polyps.

Keywords: colonoscopy, comorbidity, risk factors, colonic polyps, colonic neoplasms

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Abbreviations:

CRC: Colorectal cancer

BMI: Body mass index

T2DM: Type-2 diabetes mellitus

BBPS: Boston bowel preparation scale

FHCRC: Family history of colorectal cancer

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INTRODUCTION

Several factors have been investigated for their association with colorectal cancer (CRC). Due to inductive logic, these same factors are associated with an increased prevalence of CRC precursor lesions: colorectal polyps. For instance, smoking has been associated with both.¹ Another study highlighted in a broader sense that a healthy lifestyle is associated with a lower risk of CRC.² In this study, more than 500,000 people were analyzed regarding the impact of various factors on the incidence of CRC (e.g. body mass index – BMI, physical activity, smoking, and diet). Interestingly, they did not find statistical significance for isolated factors but rather identified an overall contribution of a healthier lifestyle towards a lower CRC incidence.

The impact of a healthy lifestyle on colorectal neoplasia can also be found in the East, but with slightly different results. In one retrospective case-control study³ the evaluation of a healthy lifestyle was based on physical activity (exercises at least three times a week), sufficient sleep (at least 8 hours per day), low red meat consumption (at most three times a week) and a high fiber consumption (at least 300 g per day). In addition, a comorbidity history index was formulated based on previously diagnosed diabetes, hyperlipidemia, inflammatory bowel disease and colorectal polyps. In this study, alcohol intake and smoking did not show any statistical difference in CRC prevalence, contradicting findings in Western literature. Comorbidities such as hyperlipidemia and diabetes have also been correlated with CRC.³

In addition to these factors, the Westernized diet has been associated with the development of CRC. Westernized diet is commonly described as a high fat, high red meat and low fiber intake. In a study by Le Marchand,⁴ Japanese descendants had an increase in incidence of CRC as soon as the first generation were born overseas (Hawaii). In a more recent case control study, O'Keefe et al⁵ studied an intervention to elucidate the extent of the dietary changes on the colonic mucosa. A cross-over of diets between African Americans and a rural population of South Africans has shown reciprocal changes in the colonic mucosa that may be associated with colorectal carcinogenesis.

Even within the same country, there are differences in the results of how and which factors influence colorectal neoplasia. For instance, type-2 diabetes mellitus (T2DM) has been associated with colorectal adenomas in a meta-analysis with high heterogeneity amongst the Asian, American and European studies (I^2 statistics from 45.7% to 52.8%).⁶ Six out of the eleven Western studies and four out of six Eastern studies found a positive correlation.

Although research investigating the epidemiology and potential mechanisms of carcinogenesis has been done, data is limited on the uniquely multiethnic and multicultural Australian population. In addition, scarce are the studies that analyze separately the contribution of such factors to individual histological polyp subtypes (i.e. adenomas and serrated polyps). We therefore embarked on a prospective study to evaluate the factors associated with colorectal neoplasia in an Australian cohort.

MATERIALS AND METHODS

Consecutive patients undergoing colonoscopy from August 2016 to January 2018 were invited to participate in the study. The colonoscopes used for the procedures were the Olympus® 190 series and performed by a single proceduralist (RS). This study has been approved by the Central Adelaide Local Health Network human research ethics committee as a low and negligible risk research through the approval number 2008128.

Patients under 18 years old and those unwilling to participate in the study were excluded. In addition, patients with total colectomy, a previous diagnosis or any endoscopic activity of inflammatory bowel disease, familial adenomatous polyposis or Peutz-Jeghers syndrome were excluded. Patients submitted to emergency colonoscopies (e.g. acute bleeding requiring endoscopic hemostasis) were also excluded since the focus of the colonoscopy would most likely not allow for the evaluation and resection of polyps. Only complete colonoscopies were included (i.e. acute angles that did not allow to progress to the caecum/ileo-colic anastomosis were excluded).

During the procedure, the quality of the bowel preparation was evaluated through the Boston bowel preparation scale (BBPS). Patients with BBPS < 6 were excluded. In patients with partial colectomy, a value for BBPS was attributed to the resected segment for comparison purposes. The attributed BBPS corresponded to the mean of the existing colonic segments (minus 0.5 when the result was a decimal).

Prior to the colonoscopy, patients were invited to participate in the research and all questions were clarified. All patients had previously received an explanatory sheet about the study, which was sent along with the bowel preparation kit. On the day of the colonoscopy, a one-page questionnaire was used to collect information on age, gender, family history of CRC (FHCRC), comorbidities and various associated factors prior to the procedure. The information was then correlated with the findings of the colonoscopy.

Habits and dietary factors were used as categorical variables (dichotomy – YES or NO). Physical activity was considered adequate if the patient exercised more than 30 minutes for 3 times a week. Red meat consumption was considered high if patients had eaten more than three times a week. Fiber consumption was conceived to be sensitive and was considered high if they had eaten more than two portions of cereals, fruits, oatmeal, legumes or vegetables per day (roughly equivalent to 30g of fiber per day). Smoking was considered positive if the patient was an active smoker regardless of the amount. Alcohol intake was considered high if greater than two standard drinks for men and one for women were consumed daily. Age and weight (through BMI) were retrieved as continuous variables but dichotomized for analysis purposes (≥ 65 years of age and 30 kg/m^2 , respectively). A FHCRC was defined by the presence of any first or second-degree relatives with CRC.

Habit questions were based on previous studies and chosen in order to simplify the patients' responses. Physical activity, alcohol intake, smoking status and red meat consumption questions were based on the previous study of Hang et al³ and the Australian National Health and Medical Research Council recommendations.⁷

The responses to the questionnaire were manually computed into an Excel database. The findings of the colonoscopy were entered alongside these. The histology results of the resected specimens were compiled into the database at a later date, once available.

The primary outcome was association of various factors with neoplastic lesions found at the present colonoscopy. Secondary outcomes were the association of various factors with presence of: conventional adenomas; neoplastic serrated polyps; any polyps (past or present); or hyperplastic polyps. The presence of any lesions (past and present) was considered when patients either had any lesions detected in prior procedures (i.e. colonoscopy for surveillance or referred for advanced

endoscopic resection); or in the current procedure for screening or symptoms.

Neoplastic lesions were defined as any conventional adenoma, sessile serrated adenoma/polyp, traditional serrated adenoma or colorectal cancer detected during the colonoscopy. Conventional adenomas were considered present when at least one adenoma (i.e. tubular adenoma, tubulovillous adenoma or villous adenoma) was detected. Neoplastic serrated polyps were considered present when any sessile serrated adenoma/polyp or traditional serrated adenoma were detected during the procedure. All colorectal neoplasia types included were confirmed by histopathology.

For the assessment of association between various factors and proposed outcomes, logistic generalized estimating equation models have been used to account for clustering on patients. Univariate analyses were performed for all factors. Those predictors with a p-value < 0.2 in the univariate regression were included in an initial multivariable regression model, one model for each outcome. Backwards elimination was then performed, removing the covariate with highest p-value one at a time until only significant predictors remained at the 0.05 level of significance. The statistical software used was SAS 9.4 (SAS Institute Inc., Cary, NC, USA). Difference of proportions was assessed with the Chi-squared test.

RESULTS

A total of 325 colonoscopies were assessed against the eligibility criteria. From those, 291 were included in the final analysis. Excluded cases consisted mainly of inflammatory bowel disease cases. During the period of the study, 26 patients had their colonoscopies repeated once and 3 had their colonoscopies repeated twice as per the number and/or complexity of the lesions found. These have been accounted for in the statistical model. The mean age of participants was 63.9 and 56% of our cohort was 65 years or older. The average BMI was 28.5 (28.3 for males and 29 for females). Cohort demographics are summarized in [Table 1] and polyp characteristics are summarized in [Table 2]. Conventional adenomas and neoplastic serrated polyps were found concurrently in only 28 (9.6%) procedures. In relation to differences in associated factors between

Table 1 Cohort demographics – n (%)

Total number of procedures	291 (100)
Male gender	156 (53.6)
Indication for the procedure^a	
Screening	73 (25.3)
Surveillance	146 (50.5)
Symptoms	70 (24.2)
Diabetes mellitus	58 (20.1)
Prophylactic aspirin	49 (17)
Hyperlipidaemia	117 (40.6)
Active smoking	68 (23.7)
High alcohol intake	42 (14.7)
Fibre intake > 30g/day	224 (78.9)
High red meat intake	137 (48.2)
Physical activity adequate	181 (64.2)
Body mass index ≥ 30	97 (33.1)
Family history of colorectal cancer positive	55 (21.1)

^a For patients referred for endoscopic resection the indication represents the index procedure.

Colorectal neoplasia associated factors

genders, the only factor that was shown to be statistically different was alcohol intake, which was lower in the female cohort [Table 3].

In the initial univariate analysis for neoplastic lesions, patients with ≥ 65 years old had 2.3 times greater odds of having a past or present polyp compared with patients with < 65 years of age. Similarly, patients with T2DM had 2.4 times greater odds of having neoplastic lesions than patients without T2DM.

Being a current smoker, being ≥ 65 years of age and the use of prophylactic aspirin were all factors found to be associated with conventional adenomas in univariate analyses. The odds were 1.8, 2.3 and 2.4 times greater, respectively. For neoplastic serrated polyps, ≥ 65 years of age, BMI ≥ 30 , T2DM and a FHCRC were factors found to have increased odds of having neoplastic serrated polyps. A statistically significant association was found between the presence of past or present polyps and age (p -value = 0.0006). Those patients who were aged 65 years or older

Table 2 Colorectal lesion occurrence and histology

Colonoscopies n (%)	Total	291 (100)
	Neoplastic lesion present	196 (67.4)
	Conventional adenoma present	168 (57.7)
	Neoplastic serrated polyp present	45 (15.5)
	Any lesion present (current procedure)	223 (76.6)
	Any lesion present (current or past procedure)	252 (86.6)
Histology n (%)	Total	483 (100)
	Hyperplastic	56 (11.6)
	Adenoma LGD	298 (61.7)
	Adenoma HGD	22 (4.6)
	SSA/P without dysplasia	75 (15.5)
	SSA/P with dysplasia	10 (2.1)
	Superficial cancer	6 (1.2)
	Invasive cancer	11 (2.3)
	Traditional serrated adenoma	1 (0.2)
Other	4 (0.8)	

LGD: low grade dysplasia, HGD: high grade dysplasia, SSA/P: sessile serrated adenoma/polyp.

Table 3 Prevalence of associated factors in enrolled participants, by gender

	Male – n (%)	Female – n (%)
Diabetes mellitus	29 (18.8)	29 (21.6)
Prophylactic aspirin	25 (16.2)	24 (17.9)
Hyperlipidemia	65 (42.2)	52 (38.8)
Active smoking	40 (26.1)	28 (20.9)
High alcohol intake*	33 (21.7)	9 (6.7)
Fiber intake > 30g/day	118 (77.6)	106 (80.3)
High red meat intake	80 (52.6)	57 (43.2)
Physical activity adequate	103 (68.2)	78 (59.5)
Body mass index ≥ 30	47 (30.7)	50 (37.3)
Family history of colorectal cancer positive	23 (16.5)	32 (26.2)

* $p < 0.01$

Table 4 Univariate logistic generalized estimating equation model analysis of association of various factors with colorectal neoplasia

Model#	Outcome	Predictor	Comparison value	OR (95% CI)	p-value
1	Neoplastic lesions	Age	≥ 65 years	2.27 (1.38 to 3.76)	<0.01
	Neoplastic lesions	T2DM	Currently on medication	2.36 (1.22 to 4.56)	<0.05
2	Conventional adenomas	Age	≥ 65 years	2.33 (1.42 to 3.80)	<0.01
	Conventional adenomas	Prophylactic aspirin	Currently on medication	2.43 (1.10 to 5.36)	<0.05
	Conventional adenomas	Smoking	Active smoking	1.84 (1.01 to 3.35)	<0.05
3	Neoplastic serrated polyps	Age	≥ 65 years	2.04 (1.02 to 4.10)	<0.05
	Neoplastic serrated polyps	T2DM	Currently on medication	3.12 (1.53 to 6.34)	<0.01
	Neoplastic serrated polyps	BMI	≥ 30	2.24 (1.16 to 4.34)	<0.05
	Neoplastic serrated polyps	FHCRC	1 st or 2 nd degree relative	2.17 (1.07 to 4.42)	<0.05
4	Any lesions (past and present)	Age	≥ 65 years	3.73 (1.75 to 7.94)	<0.01
	Any lesions (past and present)	T2DM	Currently on medication	10.98 (1.46 to 82.41)	<0.05
	Any lesions (past and present)	Hyperlipidemia	Currently on medication	2.43 (1.09 to 5.39)	<0.05
5	Hyperplastic polyps	Gender	Male	5.04 (1.10 to 23.20)	<0.05

T2DM: type 2 diabetes mellitus, BMI: body mass index, FHCRC: family history of colorectal cancer.

had odds of having a past or present polyp 3.7 times greater than patients aged less than 65 years. There was also a statistically significant association found between the presence of past or present polyps and both T2DM and hyperlipidemia. Patients who had T2DM or hyperlipidemia had odds of having a past or present polyp 11.0 and 2.4 times greater, respectively [Table 4].

In the multivariable logistic generalized estimating equation model analysis, a statistically significant association was found between the presence of neoplastic lesions and age, T2DM, gender and smoking, with each predictor controlling for each other and with adjustment for clustering on patient [Table 5]. Those patients who were ≥ 65 years old had odds of having a neoplastic lesion 2.5 times higher, patients with T2DM had odds 2.4 times higher, males had odds 1.7 times higher and current smokers had odds 2.2 times higher.

There was also a statically significant association found between the presence of past or present polyps, age and T2DM. Those patients who were aged 65 or older had 3.4 times greater odds of having a past or present polyp and patients with T2DM had odds 9.7 times higher. The associations between adenomas and age, gender and smoking were also statistically significant. Those patients who were aged 65 or older had odds of having adenomas 2.7 times higher, males had odds 1.7 times higher and current smokers had odds 2.2 times higher. Neoplastic serrated polyps' prevalence was shown to be significantly associated with T2DM and FHCRC. If these factors were present, the odds of having a neoplastic serrated polyp were 3.5 and 2.1 times greater, respectively.

Table 5 Multivariable logistic generalized estimating equation model analysis of association of various factors with colorectal neoplasia

Model#	Outcome	Predictor	Comparison value	OR (95% CI)	p-value
1	Neoplastic lesions	Age	≥ 65 years	2.51 (1.47 to 4.28)	<0.01
	Neoplastic lesions	T2DM	Currently on medication	2.39 (1.24 to 4.61)	<0.01
	Neoplastic lesions	Gender	Male	1.74 (1.03 to 2.94)	<0.05
	Neoplastic lesions	Smoking	Active smoking	2.19 (1.14 to 4.23)	<0.05
2	Conventional adenomas	Age	≥ 65 years	2.72 (1.62 to 4.58)	<0.01
	Conventional adenomas	Gender	Male	1.70 (1.03 to 2.81)	<0.05
	Conventional adenomas	Smoking	Active smoking	2.24 (1.17 to 4.27)	<0.05
3	Neoplastic serrated polyps	T2DM	Currently on medication	3.52 (1.68 to 7.35)	<0.01
	Neoplastic serrated polyps	Family history of CRC	1 st or 2 nd degree relative	2.11 (1.01 to 4.40)	<0.05
4	Any lesions (past and present)	Age	≥ 65 years	3.36 (1.56 to 7.24)	<0.01
	Any lesions (past and present)	T2DM	Currently on medication	9.66 (1.29 to 72.45)	<0.05
5	Hyperplastic polyps	Gender	Male	5.04 (1.10 to 23.20)	<0.05

T2DM: type 2 diabetes mellitus, CRC: colorectal cancer.

A subanalysis was also performed looking at factors associated with hyperplastic polyps. For both univariate and multivariate analyses, the only relevant factor associated with the presence of hyperplastic polyps was male gender [Tables 4 and 5].

DISCUSSION

This study revealed that, in a multivariable model, active smokers were 2.2 (95% CI: 1.1, 4.2) times more likely to have colorectal neoplasia than non-smokers. Several other studies have also shown smoking to be associated with colorectal neoplasia, but mainly CRC.⁸⁻¹¹ Regarding polyps, the carcinogens in tobacco are believed to increase the formation and growth rate of conventional adenomas, contributing to an estimated 12% of CRC deaths.¹² In this study, although smoking was associated with conventional adenomas, it was not associated with neoplastic serrated polyps. Hence, tobacco appears to predominantly affect the adenoma-carcinoma pathway. Our results are in contrast to another study,¹³ which found that in addition to adenomas (RR 1.29, 95% CI: 1.11, 1.49), smoking was also associated with serrated polyps (RR 2.27, 95% CI: 1.68, 3.06). However, Figueiredo et al¹³ considered all serrated polyps for their outcome, whether neoplastic or not. In addition, their increase of serrated polyps was only found when looking at left colon serrated polyps, which are known to rarely be neoplastic.

In a multivariable model, patients with T2DM had 2.4 (95% CI: 1.2, 4.6) times an increased risk of colorectal neoplasia. This concurs with the literature which found that both CRC (RR

1.21, 1.30) and neoplastic polyps (RR 1.52) prevalence are associated with T2DM.¹⁴⁻¹⁶ Interestingly, the association in our study was specifically with serrated neoplastic lesions. This theory is supported by the meta-analysis of Yu et al¹⁶ From all included studies the one that revealed the highest RR was also the only one that included solely sessile serrated adenoma/polyps.

It has been suggested that the hyperinsulinemia and free IGF-1 in insulin resistant T2DM patients may promote the proliferation of colonic epithelial cells, possibly having a tumorigenic effect.¹⁷⁻¹⁹ A study by Yang et al²⁰ found that T2DM with insulin use ≥ 1 -year was associated with an increased risk of CRC (2.1, 95% CI 1.20, 3.40) as compared to T2DM not managed with insulin. Although a hypothetical mechanism was considered, our results did not show a significant difference in colorectal neoplasia when comparing T2DM patients using insulin as compared to those not using insulin (OR 1.42, 95% CI: 0.36, 5.57). However, this could possibly be due to a type II error.

Our results have some possible public health implications. An estimated 1.7 million Australians suffer from diabetes in addition to the disease being the fastest growing chronic condition in the country, surpassing heart disease and cancer.²¹ CRC was the second most commonly diagnosed cancer in Australia in 2018 (behind breast in females and prostate in males), contributing to over 4,000 deaths in one year.²² As the prevalence of diabetes increases, it may contribute to more cases of CRC and its precursors. Therefore, the addition of associated factors such as T2DM to the current guidelines could potentially allow risk stratification in screening and surveillance colonoscopy protocols.

As expected, men and those older than 65 had a 1.7 (95% CI: 1.03, 2.9) and 2.5 (95% CI: 1.5, 4.3) higher risk of presenting with colorectal neoplasia respectively, in a multivariable model. This is in line with other studies that show a significantly higher incidence of CRC in the 60+ age group^{12,23} and in males.^{24,25}

There are some limitations to our study. The sample size was limited, and it was based at a single center. In addition, although the assessment of diet through simple questions facilitated the acquisition of data within the limited timeframe prior to the procedure; it was a less objective assessment compared to a standardized nutritional questionnaire. Nevertheless, to the best of our knowledge, this is the first study looking at factors associated with colorectal neoplasia in an Australian setting. Although the lack of statistical difference might be due to the small sample size, the differences shown to be statistically significant add valuable information to the field and may help us better understand how these factors impact on different neoplastic lesions.

In conclusion, a significant association was found between the presence of neoplastic lesions and age ≥ 65 , T2DM, male gender and smoking. The predictors found for conventional adenomas (older age, male gender and smoking) were different from the predictors for neoplastic serrated polyps (T2DM and FHCR).

CONFLICT OF INTEREST STATEMENT

All authors declare no conflicts of interest for this paper.

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