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Research Article

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Colorectal Cancer Risk Following Adenoma Removal: A Large Prospective Population-Based Cohort Study

Helen G. Coleman[1], Maurice B. Loughrey[2], Liam J. Murray[1], Brian T. Johnston[3], Anna T. Gavin[1,4], Martha J. Shrubsole[5], Shivaram K. Bhat[1], Patrick B. Allen[6], Vivienne McConnell[7], and Marie M. Cantwell[1]

Abstract

Background: Randomized controlled trials have demonstrated significant reductions in colorectal cancer incidence and mortality associated with polypectomy. However, little is known about whether polypectomy is effective at reducing colorectal cancer risk in routine clinical practice. The aim of this investigation was to quantify colorectal cancer risk following polypectomy in a large prospective population-based cohort study.

Methods: Patients with incident colorectal polyps between 2000 and 2005 in Northern Ireland were identified via electronic pathology reports received to the Northern Ireland Cancer Registry. Patients were matched to the Northern Ireland Cancer Registry to detect colorectal cancer and deaths up to December 31, 2010. Colorectal cancer standardized incidence ratios (SIR) were calculated and Cox proportional hazards modeling applied to determine colorectal cancer risk.

Results: During 44,724 person-years of follow-up, 193 colorectal cancer cases were diagnosed among 6,972 adenoma patients, representing an annual progression rate of 0.43%. Colorectal cancer risk was significantly elevated in patients who had an adenoma removed (SIR, 2.85; 95% CI, 2.61–3.25) compared with the general population. Male sex, older age, rectal site, and villous architecture were associated with an increased colorectal cancer risk in adenoma patients. Further analysis suggested that not having a full colonoscopy performed at, or following, incident polypectomy contributed to the excess colorectal cancer risk.

Conclusions: Colorectal cancer risk was elevated in individuals following polypectomy for adenoma, outside of screening programs.

Impact: This finding emphasizes the need for full colonoscopy and adenoma clearance, and appropriate surveillance, after endoscopic diagnosis of adenoma. *Cancer Epidemiol Biomarkers Prev; 24(9); 1373–80. ©2015 AACR.*

Introduction

In the United Kingdom, colorectal cancer is the fourth most common incident cancer and second most common cause of cancer-related death (1). The United Kingdom has inferior colorectal cancer survival rates to comparable countries, commonly attributed to later clinical presentation (2, 3). Colorectal cancer typically originates from precancerous colorectal polyps, providing an opportunity for prevention if detected early and successfully excised.

The vast majority of colorectal polyps are either adenomas or hyperplastic polyps (4). Adenomas are dysplastic polyps, which can progress via the adenoma–carcinoma sequence to invasive cancer. Hyperplastic polyps are classified within the serrated group of colorectal polyps, and are traditionally considered benign. A related subtype of serrated polyps, namely sessile serrated polyps (also known as sessile serrated adenomas), may progress to carcinoma via the serrated carcinogenesis pathway, (5, 6) but these are relatively rare (7). Individuals who have only hyperplastic polyps removed at endoscopy are not typically entered into surveillance (8). Individuals with adenomas detected will usually be entered into a surveillance regime at an interval of 1, 3, or 5 years primarily depending on the number and size of adenomas detected or genetic predisposition to colorectal cancer (8, 9).

The ultimate aim of clearing the bowel of adenomas, and entering patients into surveillance, is to reduce colorectal cancer risk. Building upon the historic findings of Winawer and colleagues (10), several recent randomized controlled trials (11–14) and population-based case–control studies (15, 16) have demonstrated the success of polypectomy in reducing colorectal cancer risk. The U.S. Prostate, Lung, Colorectal, and Ovarian cancer screening trial has reported a significant 21% reduced risk

[1]Cancer Epidemiology and Health Services Research Group, Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland [2]Department of Pathology, Belfast Health and Social Care Trust, Belfast, Northern Ireland. [3]Department of Gastroenterology, Belfast Health and Social Care Trust, Belfast, Northern Ireland. [4]Northern Ireland Cancer Registry, Centre for Public Health, Queen's University, Belfast, Northern Ireland. [5]Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt University School of Medicine, Nashville, Tennessee. [6]Department of Gastroenterology, Ulster Hospital, Dundonald, South Eastern Health and Social Care Trust, Northern Ireland. [7]Northern Ireland Regional Genetics Service, Belfast Health and Social Care Trust, Belfast, Northern Ireland.

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Corresponding Author: Helen G. Coleman, Queen's University Belfast, ICS-B Building, RVH Site, Grosvenor Road, Belfast BT12 6BJ, Northern Ireland. Phone: 44-2890635049; Fax: 44-2890635900; E-mail: h.coleman@qub.ac.uk

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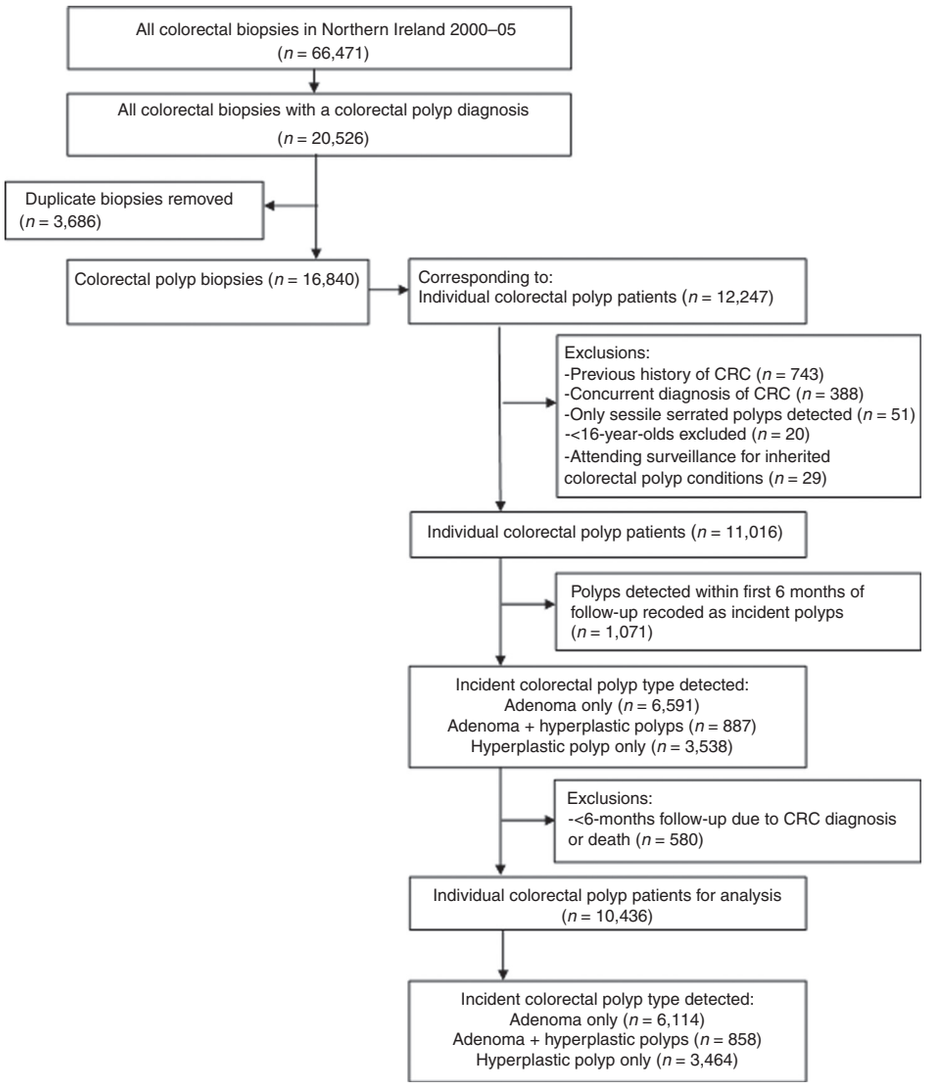

Figure 1.
Development of the Northern Ireland colorectal polyp register 2000–05. CRC, colorectal cancer.

of colorectal cancer among the intervention arm who underwent flexible sigmoidoscopy at baseline plus 3 or 5 years later, compared with usual care (11). A 'one-off' flexible sigmoidoscopy was also effective at reducing colorectal cancer risk by 23% in a UK trial (12), whereas similar reductions were observed in Italian, but not Norwegian, trials (13, 14).

However, little is known about whether polypectomy is effective at reducing colorectal cancer risk in routine clinical practice. The aforementioned trials (11–14) and case–control studies (15, 16) may incur selection bias due to modest response rates limiting the likelihood of participants being representative of the general population. Few studies have investigated colorectal cancer risk following polypectomy in the general population. A French study observed a 2.2-fold greater incidence of colorectal cancer among advanced adenoma patients compared with the general population (17), whereas a large Dutch study concluded that excess colorectal cancer risk in adenoma patients was limited to the first few years of follow-up (18). In addition, given the enhanced opportunity for polyp detection within bowel cancer screening programs (19, 20), the appropriate clinical management of patients following polypectomy is even more pertinent.

The aim of this investigation was to quantify colorectal cancer risk following polypectomy of adenomas in a large population-based study.

Materials and Methods

Subject classification

The Northern Ireland colorectal polyp register (NICPR) was derived from electronic pathology reports relating to all colorectal biopsies within Northern Ireland between 2000 and 2005. The NICPR has ethical approval from ORECNI: 10/NIR02/53. This timeframe precedes bowel cancer screening in this region, and therefore reflects clinical investigation of a symptomatic population. As outlined in Fig. 1, relevant SNOMED morphology codes for adenomas and hyperplastic polyps were extracted. Few polyps were diagnosed or coded as sessile serrated polyps during this time period, and therefore these were excluded from analysis.

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Individuals ages <16 years were also removed. We applied two strategies for identifying and excluding patients who may be genetically predisposed to colorectal cancer due to polyposis syndromes. First, patients were removed from the NICPR if they attended a genetic follow-up service at the Belfast Health and Social Care Trust (the sole referral center in Northern Ireland). Second, we conducted a medical note review as part of a nested case–control study (described in detail below) to identify participants with a personal or family history of colorectal polyps or polyposis syndromes.

Patients were categorized into an "adenoma register" if their incident polyp was recorded as an adenomatous polyp(s) with or without a concurrent hyperplastic polyp(s) diagnosis. Patients who only received a hyperplastic polyp diagnosis were grouped into a "hyperplastic polyp register." SNOMED coding was used to identify tubular, tubulovillous, or villous adenoma subtypes. Information on polyp size was not readily available, and so patients with "advanced risk" adenomas were considered to be those with multiple adenomas of any histological type or at least one adenoma including a villous component, that is, villous or tubulovillous. In order to minimize misclassification of polyps detected but not removed at first investigation, all polyps detected within 6 months of the baseline polyp were reclassified as "incident" polyps. Subsequent polyps were those diagnosed at least 6 months after incident polyps, and up to December 31, 2005.

Outcome classification

The Northern Ireland Cancer Registry collects information on all cancer diagnoses since 1993. All individuals diagnosed with colorectal cancer (ICD-10 codes C18-C20) up to December 31, 2010, were matched on the basis of name, date of birth, and/or address to the NICPR. Individuals with a previous or concurrent colorectal cancer diagnosis were excluded from the NICPR. Colorectal cancer cases diagnosed at least 6 months after their incident polyp were considered to be incident colorectal cancer, and were considered for further case note review as part of a nested case–control study, as detailed below. The NICPR was also matched to death records supplied by the Northern Ireland Registrar General's Office to the Northern Ireland Cancer Registry to detect patients who died by December 31, 2010.

Nested case–control study

Patients who developed colorectal cancer at least 6 months post-incident polyp diagnosis were included in a nested case–control study. Controls were matched 1:1 to colorectal cancer cases by age (±1 year), sex, year of incident polyp diagnosis, and were alive at the time of their matched cases' colorectal cancer diagnosis. Tumor verification officers reviewed hospital case notes for information on all colorectal cancer and polyp diagnoses, polyp characteristics (including size, number, and dysplasia grade), personal and family history of chronic bowel diseases, and all lower gastrointestinal investigations conducted (including endoscopies) from 1 year prior to incident polyp diagnosis up to end of follow-up. A small number of individuals who were found to have a personal history of polyposis syndromes (or a family history of colorectal polyps as a proxy for an undiagnosed polyposis syndrome) were excluded from further nested case–control study analysis due to the likelihood that they are genetically predisposed to colorectal cancer. We did not exclude individuals reporting a family history of colorectal cancer, because only a small proportion (5%–10%; 21) of these cases are likely to be due to genetic conditions and a known family history may simply reflect shared lifestyle or other nonhereditary colorectal cancer risk factors between family members. Cases for whom we were able to retrieve notes to enable inclusion within the case–control study did not differ from those not included with respect to age, sex, polyp location, morphology, or advanced status, and are therefore representative of the entire colorectal cancer case set.

Statistical analysis

Patients were followed up from the date of their incident polyp diagnosis (excluding the first 6 months of follow-up) until their date of colorectal cancer diagnosis, date of death or December 31, 2010. Descriptive characteristics were compared using independent *t*-tests and χ^2 tests for continuous and categorical variables, respectively. Individuals with less than 6 months follow-up were excluded from analysis. Colorectal cancer incidence was calculated per 100 person-years of follow-up, comparing observed incidence with that of expected incidence in the Northern Ireland population between 2000 and 2010. Cox proportional hazards models were applied to investigate the association between colorectal cancer risk and demographics or incident polyp characteristics. Stratified analysis was conducted by these variables to explore effect modification. Assumptions for Cox proportional hazards models were checked by visual inspection of Kaplan–Meier plots. Standardized colorectal cancer incidence ratios (SIR) and corresponding 95% confidence intervals (CI) were analyzed per 100,000 population, and separately for males and females. Sensitivity analysis was performed after excluding those with less than 1 year of follow-up. For the nested case–control study, colorectal cancer risk was assessed between comparative groups by applying conditional logistic regression analysis to generate odds ratios (OR) and 95% CI. Statistical analysis was conducted using Intercooled Stata version 11.0 (StataCorp).

Results

Over a 6-year time period, $n = 6{,}972$ individuals had a least one adenoma removed at their index colonoscopic investigation (Fig. 1). There was a slight male predominance for adenoma patients, and the mean age at adenoma removal was 62.3 years. The majority of adenomas were detected and removed from the colon, and 22% of individuals had multiple adenomas removed at their first investigation in this time period (Table 1).

During a total of 44,724 person-years of follow-up, 193 patients were diagnosed with incident colorectal cancer. The rate of progression was relatively stable over time, and was consistently higher in males than females (Fig. 2). Over this period, 0.43% of adenoma patients developed colorectal cancer each year, as shown in Table 2. Colorectal cancer risk was significantly elevated in males and in individuals aged 60 years or older with adenomas. Rectal adenoma patients had an increased colorectal cancer risk (HR, 1.70; 95% CI, 1.27–2.28) compared with those who had only colonic adenomas excised. No colorectal cancer developed in patients who had adenomas removed from both the colon and rectum. Those with tubulovillous or villous adenomas were more likely to develop colorectal cancer compared with those with tubular adenomas (HR, 1.51; 95% CI, 1.02–2.23).

Several factors were associated with reduced risk of colorectal cancer among adenoma cases, including being diagnosed with concurrent hyperplastic polyps (HR, 0.45; 95% CI, 0.24–0.82) or

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Table 1. Characteristics of individuals diagnosed with incident colorectal adenomas in Northern Ireland 2000–2005

Variable	Adenoma[a] register $n = 6,972$ (%)[b]
Sex	
Female	3,157 (45.3)
Male	3,815 (54.7)
Age at diagnosis (years, mean ± SD)	62.7 ± 13.1
Age groups at diagnosis (years)	
16–<50	1,237 (17.7)
50–<60	1,609 (23.1)
60–<70	1,916 (27.5)
70–<80	1,613 (23.1)
≥80	597 (8.6)
Year of diagnosis	
2000	1,004 (14.4)
2001	990 (14.2)
2002	1,016 (14.6)
2003	1,280 (18.4)
2004	1,278 (18.3)
2005	1,404 (20.1)
Topography of index polyp(s)	
Colon only	4,815 (69.1)
Rectum only	1,687 (24.2)
Colon and rectum	470 (6.7)
Number of incident polyps[a]	
1	5,414 (77.7)
≥2	1,558 (22.4)
Adenoma histology[c]	
Tubular only	1,771 (25.4)
Villous/tubulovillous	3,368 (48.3)
Unspecified	1,833 (26.3)
Advanced adenoma[d]	3,819 (54.8)
Subsequent adenoma[e]	870 (12.5)
Subsequent hyperplastic polyp[e]	447 (6.4)

[a]Incorporates $n = 858$ individuals diagnosed with concurrent hyperplastic polyps as outlined in Fig. 1. These are excluded from the ≥2 polyp number category unless multiple adenomas were diagnosed.
[b]Percentages may not total 100 due to rounding.
[c]Individuals with ≥1 villous or tubulovillous adenoma were classified as villous/tubulovillous, even if they also had a tubular adenoma at incident diagnosis.
[d]Individuals with multiple adenomas or ≥1 villous/tubulovillous adenomas were classified as advanced. The polyp register did not contain detailed information on polyp size.
[e]Subsequent defined as ever diagnosis ≥6 months after incident polyps and up to date of colorectal cancer diagnosis or end of December 31, 2005.

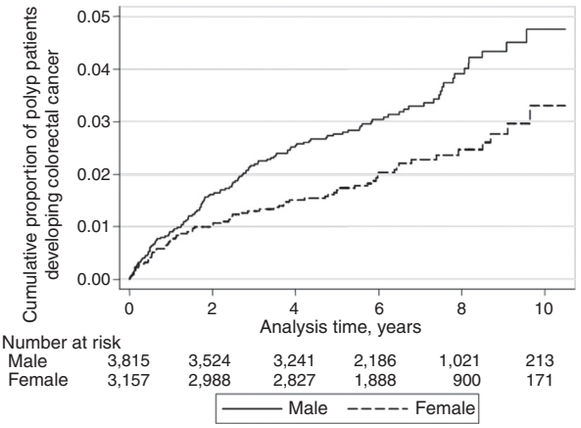

Figure 2.
Kaplan–Meier plot of the cumulative proportion of incident colorectal adenoma patients developing colorectal cancer, stratified by sex.

subsequent polyps (Table 2). Individuals diagnosed with multiple incident adenomas also had a decreased risk of colorectal cancer (HR, 0.67; 95% CI, 0.45–0.97). Sensitivity analysis removing the first year of follow-up revealed largely similar results (Supplementary Table S1). As shown in Table 2, the risk of progression to colorectal cancer was lower in patients diagnosed with only hyperplastic polyps (0.17% per year), compared with adenoma patients. Colorectal cancer risk in hyperplastic polyp patients did not differ significantly by sex, polyp location, or multiplicity; however, individuals aged 60-<80 years were at significantly increased risk of colorectal cancer compared with younger patients (data not shown).

As outlined in Table 3, individuals diagnosed with adenomas were almost three times more likely to develop colorectal cancer than the general population (SIR, 2.85; 95% CI, 2.61–3.25). This heightened risk was observed in both males and females, for those with advanced adenomas, and after excluding cases in the first year of follow-up. Unexpectedly, hyperplastic polyp patients also had an increased colorectal cancer risk compared with the general population (SIR, 1.79; 95% CI, 1.45–2.33), which did not alter in sensitivity analysis excluding incident hyperplastic polyp patients who had a subsequent adenoma (SIR, 1.80; 95% CI, 1.46–2.36). Overall, an excess of 125 and 18 colorectal cancer cases developed among adenoma and hyperplastic polyp patients, respectively.

A *post hoc* nested case–control study was conducted amongst colorectal cancer cases arising in adenoma and hyperplastic polyp cases ($n = 193$, 82.5%) and matched controls whose medical notes were available for review, to determine further factors that may explain the excess colorectal cancer risk. A small number of colorectal cancer cases were identified to have a personal history of polyposis syndromes ($n = 3$) or family history of colorectal polyps ($n = 7$), or both ($n = 1$) and were excluded from further analysis since they are likely to be genetically predisposed to a greater colorectal cancer risk, leaving $n = 148$ case–control pairs in the remaining adenoma analysis and $n = 34$ pairs in the hyperplastic polyp analysis. As shown in Table 4, a small proportion of excess colorectal cancer risk could be attributed to concurrent inflammatory bowel disease (OR, 2.25; 95% CI, 0.98–5.17). Patients with large or right-sided incident polyps or adenomas with high-grade dysplasia had nonsignificantly increased risks of developing colorectal cancer.

Conversely, those with multiple adenomas, a colorectal cancer family history or an adenoma removed prior to the initiation of our study period (and therefore potentially undergoing surveillance) did not have an increased colorectal cancer risk. Adenoma patients who had a full colonoscopy during the follow-up period had a nonsignificant reduced risk of colorectal cancer, particularly if they had multiple (two or more) full colonoscopies performed (OR, 0.59; 95% CI, 0.32–1.09). If patients had attended for investigative procedures other than full colonoscopy (e.g., sigmoidoscopy or barium enema), they had a significant increased risk of colorectal cancer (OR, 2.18; 95% CI, 1.32–3.60). In addition, individuals who did not attend for a planned procedure were at an increased risk of colorectal cancer, which was exaggerated if multiple appointments were missed (Table 4).

Nonsignificant increased colorectal cancer risks were observed for individuals with multiple and/or right-sided hyperplastic polyps, and those who did not attend for a planned follow-up investigation (data not shown).

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Table 2. Colorectal cancer risk at least 6 months after incident colorectal adenoma diagnosis

Group	No. cases	Person-years follow-up	No. colorectal cancers	Incidence, % per year (95% CI)	Adjusted[a] hazard ratio (95% CI)
Adenoma register					
All	6,972	44,724	193	0.43 (0.37–0.50)	N/A
Sex					
Female	3,157	20,656	68	0.33 (0.26–0.42)	1.00
Male	3,815	24,068	125	0.52 (0.43–0.62)	1.69 (1.26–2.27)
Age groups (years)					
<50	1,237	8,817	18	0.20 (0.12–0.32)	1.00
50–<60	1,609	11,186	29	0.26 (0.17–0.37)	1.27 (0.71–2.29)
60–<70	1,916	12,529	51	0.41 (0.30–0.53)	1.99 (1.16–3.41)
70–<80	1,613	9,414	60	0.64 (0.49–0.82)	3.10 (1.83–5.26)
≥80	597	2,778	35	1.26 (0.88–1.75)	6.16 (3.48–10.91)
Topography of index polyp(s)					
Colon	4,815	30,686	120	0.39 (0.32–0.47)	1.00
Rectum	1,687	11,042	73	0.66 (0.52–0.83)	1.70 (1.27–2.28)
Colon and rectum	470	2,997	0	0.00 (0.00–0.00)	/
No. incident adenomas					
1	5,414	34,864	161	0.46 (0.39–0.54)	1.00
≥2	1,558	9,861	32	0.32 (0.22–0.46)	0.67 (0.45–0.97)
Morphology[b]					
Tubular only	1,771	11,524	36	0.31 (0.22–0.43)	1.00
Villous/tubulovillous	3,368	21,508	97	0.45 (0.37–0.55)	1.51 (1.02–2.23)
Unspecified	1,833	11,692	60	0.51 (0.39–0.66)	1.68 (1.11–2.54)
Advanced adenomas[c]	3,819	24,373	105	0.43 (0.35–0.52)	1.13 (0.83–1.54)
Concurrent hyperplastic polyp(s)					
Adenoma only	6,114	39,051	182	0.47 (0.40–0.54)	1.00
Adenoma + hyperplastic	858	5,674	11	0.19 (0.10–0.35)	0.45 (0.24–0.82)
Subsequent adenoma[d]	870	6,572	20	0.30 (0.19–0.47)	0.72 (0.45–1.16)
Subsequent hyperplastic polyp[d]	447	3,507	4	0.11 (0.03–0.29)	0.31 (0.11–0.85)
Hyperplastic register					
All	3,439	21,807	38	0.17 (0.12–0.24)	N/A

[a]Adjusted for age at incident polyp diagnosis (<50, 50–<60, 60–<70, 70–<80, ≥80 years), sex, year of incident polyp diagnosis (2000–2005), number of incident polyps diagnosed (1, ≥2), and subsequent adenoma diagnosed (yes/no).
[b]Individuals with ≥1 villous or tubulovillous adenoma were classified as villous/tubulovillous, even if they also had a tubular adenoma at incident diagnosis.
[c]Individuals with multiple adenomas or ≥1 villous/tubulovillous adenomas were classified as advanced. The polyp register did not contain detailed information on polyp size.
[d]Subsequent defined as ever diagnosis ≥6 months after incident polyps and up to date of colorectal cancer diagnosis or end of December 31, 2005.

Discussion

Overall, annual colorectal cancer risk among individuals following polypectomy of adenomas in the nonscreening setting is 0.43%. Despite undergoing polypectomy, colorectal cancer risk is significantly elevated for incident adenoma patients compared with the general population.

The increased risk of colorectal cancer following adenoma removal observed in our study is in line with findings from a French study (17). In their analysis of 5,779 adenoma patients diagnosed between 1990 and 1999, 87 colorectal cancer were diagnosed, resulting in an SIR of 2.23 (95% CI, 1.67–2.92) for advanced adenomas (17). As a result of further case note review, a small proportion of colorectal cancer cases in this study were found to be associated with genetic predisposition (6.9% overall, and 8.5% in advanced adenoma cases). Applying these proportions to our overall SIR estimates would result in SIR of 2.65 and

Table 3. Standardized incidence ratios of colorectal cancer in individuals diagnosed with colorectal adenomas

Group	No. cases	No. CRC expected	No. CRC observed	SIR (95% CI)
Adenomas[a]				
All	6,972	68	193	2.85 (2.61-3.25)
Female	3,157	25	68	2.69 (2.30-3.33)
Male	3,815	45	125	2.76 (2.47-3.25)
Advanced adenomas[b]	3,819	38	105	1.75 (2.43-3.28)
All, excluding CRC in 1st year of follow-up	6,834	68	157	2.32 (2.10-2.69)
Hyperplastic polyps				
All	3,464	23	41	1.79 (1.34-2.14)
Female	1,668	9	17	1.89 (1.34-2.78)
Male	1,796	14	24	1.67 (1.26-2.34)
No subsequent adenoma	3,382	22	40	1.80 (1.46-2.36)

Abbreviation: CRC, colorectal cancer.
[a]Incorporates $n = 858$ individuals diagnosed with concurrent hyperplastic polyps as outlined in Fig. 1.
[b]Individuals with multiple adenomas or ≥1 villous/tubulovillous adenomas were classified as advanced. The polyp register did not contain detailed information on polyp size.

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Table 4. Colorectal cancer risk factors from a case note review of patients with colorectal adenoma who developed colorectal cancer and matched controls

	Adenoma patients		
Factor	**Controls *n* = 148 (%)**	**CRC cases *n* = 148 (%)**	**Odds ratio[a] (95% CI)**
Previous adenoma before 2000			
No/unknown	132 (89.2)	136 (91.9)	1.00
Yes	16 (10.8)	12 (8.1)	0.69 (0.30-1.62)
Personal history of IBD			
No/unknown	137 (92.6)	127 (85.8)	1.00
Yes	11 (7.4)	21 (14.2)	2.25 (0.98-5.17)
Family history of CRC			
No/unknown	127 (85.8)	130 (87.8)	1.00
Yes	21 (14.2)	18 (12.2)	0.83 (0.42-1.65)
Presence of HGD			
No/unknown	135 (91.2)	121 (81.8)	1.00
Yes	13 (8.8)	27 (18.2)	3.33 (1.34-8.30)
No. incident polyps			
1	94 (63.5)	105 (71.0)	1.00
≥2	54 (36.5)	43 (29.0)	0.70 (0.43-1.16)
Right-sided polyp[b]			
No/unknown	134 (85.4)	124 (83.8)	1.00
Yes, ≥1 right-sided	23 (14.7)	24 (16.2)	1.22 (0.66-2.28)
Polyp size			
Small/unknown	112 (75.7)	103 (69.6)	1.00
Large (≥1 cm)	36 (24.3)	45 (30.4)	1.35 (0.81-2.24)
Full colonoscopy[c]			
No/unknown	37 (25.0)	50 (33.8)	1.00
Yes, 1	49 (33.1)	45 (30.4)	0.66 (0.36-1.21)
Yes, ≥2	62 (41.9)	53 (35.8)	0.59 (0.32-1.09)
Any other investigations[d]			
No/unknown	23 (15.5)	18 (12.2)	1.20 (0.58-2.47)
Yes, 1[e]	62 (41.9)	38 (25.7)	1.00
Yes, ≥2	63 (42.6)	92 (62.2)	2.18 (1.32-3.60)
Did not attend for planned follow-up procedure			
No/unknown	137 (92.6)	132 (89.2)	1.00
Yes	10 (6.8)	13 (8.8)	1.45 (0.62-3.41)
Yes, missed >1 procedure	1 (0.7)	3 (2.0)	3.64 (0.36-37.01)

Abbreviations: CRC, colorectal cancer; HGD, high-grade dysplasia; IBD, inflammatory bowel disease.

[a]Adjusted for matching criteria (age, sex, incident polyp type adenoma/hyperplastic) and year of diagnosis at incident polyp.

[b]Includes polyps detected in cecum, ascending colon, hepatic flexure, and transverse colon.

[c]Number of full colonoscopies performed within 1 year prior to incident polyp diagnosis and before censor date (CRC diagnosis or matched follow-up time for controls).

[d]Any other investigative procedures (excluding full colonoscopy), including incomplete or unspecified colonoscopy, proctoscopy, rigid or flexible sigmoidoscopy, or barium enema performed within 1 year prior to incident polyp diagnosis.

[e]Chosen as reference category to reflect that many individuals attended for a sigmoidoscopy or other non-full colonoscopy investigation at their first investigation, which was then followed up by a full colonoscopy.

2.53 for all and advanced adenomas, respectively, and are more comparable with the methods in the French study (17). The largest study to date, published from a Dutch population, only observed an elevated SIR (2.8; 95% CI, 2.5–3.1) in the second and third year of follow-up, which was then attenuated in later years (18). This contrasts with our study findings, which illustrate a consistently increased colorectal cancer risk over a prolonged time period. Earlier population-based studies of smaller sample size, tended to observe either no association or a reduced risk of colorectal cancer following adenoma removal. (15, 16, 22) Randomized controlled trials of flexible sigmoidoscopy have also mostly demonstrated a reduction in colorectal cancer incidence (11, 12, 14). Our findings indicate that the benefits seen for polyp removal in the tightly controlled environment of trials and screened populations may not be replicated in the general population who are more likely to be symptomatic when presenting for clinical investigation.

As expected, being male or ages 60 years or older was associated with an increased risk of colorectal cancer following adenoma removal (23, 24). Individuals whose incident adenomas contained a villous component also had increased colorectal cancer risk, which is consistent with previous reports (23). Other factors that would be expected to increase colorectal cancer risk, including a personal history of inflammatory bowel disease, presence of high-grade dysplasia in the adenomas, and large adenoma size (9, 25) were directly associated with colorectal cancer risk in the detailed case note review aspect of our study. All of these findings are reassuring for the robustness of our data, but collectively, these factors only account for a relatively small proportion of the excess colorectal cancer cases found in this population.

Several factors indirectly suggested that incomplete clearance of adenomas from the bowel may have led to the higher future colorectal cancer risk, which is consistent with previous study findings. (26–29) First, having only rectal adenomas diagnosed was associated with an increased risk of colorectal cancer, implying the colon may not have been examined. No colorectal cancer occurred among individuals who had adenomas diagnosed in both the colon and rectum. Similarly, having multiple adenomas removed was inversely associated with colorectal cancer risk. Finally, having concurrent adenoma and hyperplastic polyp

removal at incident polypectomy (which suggests more thorough primary clearance of the bowel) or subsequent hyperplastic polyp detection (which indicates follow-up endoscopy) was associated with a reduced risk of colorectal cancer. This was also corroborated by results from the case note review, in which individuals undergoing a full colonoscopy had decreased risks of colorectal cancer, whereas patients who had other investigative procedures such as incomplete colonoscopy, flexible sigmoidoscopy, or barium enema had an increased risk of colorectal cancer. These findings have implications for current surveillance guidelines following polypectomy (9). Our results suggest that a significant proportion of patients diagnosed with colorectal adenoma do not undergo full colonoscopy and adenoma clearance, and this incurs an increased risk of colorectal cancer. The reasons for this are unclear but merit further consideration. Although patient choice is foremost in decision making, understanding potential barriers for colonoscopy compliance is an important area for future research. Having multiple full colonoscopies following incident adenoma removal was inversely associated with colorectal cancer risk, which argues for the benefit of continued surveillance (30). The increased yield of adenomas and colorectal cancer when performing full colonoscopy compared with other procedures is well established (31–33).

We also observed an unexpected increased colorectal cancer risk among individuals having only hyperplastic polyps removed. The potential for hyperplastic polyps to be a marker of adenomas has been previously debated (34, 35). Our results do not support this finding, since an increased colorectal cancer risk remained when individuals with subsequent adenomas were removed from analysis. However, we were unable to account for adenomas detected after 2005 and undetected concurrent or subsequent adenomas may still explain the excess colorectal cancer risk seen. Sessile serrated polyps represent another subset of serrated polyps, much rarer than hyperplastic polyps, and have only been well described in recent years (36). Sessile serrated polyps are more common in the proximal colon, are often multiple, are larger than typical hyperplastic polyps, and are now accepted as the precursors to serrated pathway colorectal cancers (37, 38). Sessile serrated polyps were not frequently reported by pathologists during this study period and it is likely many such polyps were misdiagnosed as hyperplastic polyps (36, 39). This is supported by our findings that multiple and right-sided "hyperplastic polyps" carried an increased risk of colorectal cancer progression.

Our study has several strengths, including its large size, length of follow-up and relevance to current practice, given the timeframe of adenoma patients studied. The population-based nature of the study is important to emphasize, demonstrating colorectal cancer risk following polypectomy in a "real world" setting. This is the first insight into this association in a UK population, among whom health care is free at the point of access. Northern Ireland has a relatively stable population with limited migration (40), therefore the completeness of passive follow-up is excellent. Furthermore, our results were not diluted with bowel cancer screening-detected adenomas/cancers because a screening programme only commenced in mid-2010. This study does have some limitations that should be considered. In the NICPR, we did not have information on polyps diagnosed prior to 2000 or after 2005, or information on polyp size, or detailed polyp topography. However, we overcame these limitations by conducting a detailed note review in a nested case–control study. The number of polyps in patients with more than one polyp was also underestimated due to the potential for SNOMED codes to have been entered only once by the reporting pathologist, if a patient had multiple polyps diagnosed of the same histological type at one episode. Comparison with the case note review data suggests that approximately 10% of patients with multiple adenomas were misclassified as singular in the overall register.

In conclusion, this large population-based study demonstrates that colorectal cancer risk remains significantly higher than that of the general population following adenoma removal, outside of screening programs. Our findings suggest the increased colorectal cancer risk may be partially due to incomplete examination and/or adherence to follow-up colonoscopies. There is a need for full colonoscopy and adenoma clearance after a diagnosis of colorectal adenoma to reduce risk of subsequent colorectal cancer. Further research is required to identify optimal surveillance protocols, and adherence to these, following adenoma removal.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.B. Loughrey, L.J. Murray, B.T. Johnston, P.B. Allen, M.M. Cantwell

Development of methodology: H.G. Coleman, L.J. Murray, B.T. Johnston, P.B. Allen, M.M. Cantwell

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): H.G. Coleman, L.J. Murray, A.T. Gavin, M.M. Cantwell

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.G. Coleman, M.B. Loughrey, L.J. Murray, B.T. Johnston, A.T. Gavin, M.J. Shrubsole, S.K. Bhat, M.M. Cantwell

Writing, review, and/or revision of the manuscript: H.G. Coleman, M.B. Loughrey, L.J. Murray, B.T. Johnston, A.T. Gavin, M.J. Shrubsole, S.K. Bhat, V. McConnell, M.M. Cantwell

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.G. Coleman, A.T. Gavin, M.M. Cantwell

Study supervision: H.G. Coleman, B.T. Johnston, M.M. Cantwell

Other (the genetic aspect of this manuscript and patients known to the regional genetic service whose pathology of adenoma, etc., was genetic and was integral to the manuscript interpretation as opposed to sporadic adenomas): V. McConnell

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