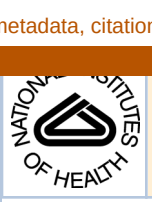

Published in final edited form as:

Am J Gastroenterol. 2012 May ; 107(5): 770–778. doi:10.1038/ajg.2012.52.

Cancer risks for relatives of patients with serrated polyposis

Aung Ko Win[1,*], **Rhiannon J. Walters**[2,*], **Daniel D. Buchanan**[2,3], **Mark A. Jenkins**[1], **Kevin Sweet**[4], **Wendy L. Frankel**[5], **Albert de la Chapelle**[6], **Diane M. McKeone**[2], **Michael D. Walsh**[2,3], **Mark Clendenning**[2], **Sally-Ann Pearson**[2], **Erika Pavluk**[2], **Belinda Nagler**[2], **John L. Hopper**[1], **Michael R. Gattas**[7], **Jack Goldblatt**[8,9], **Jill George**[9], **Graeme K. Suthers**[10,11], **Kerry D. Phillips**[11], **Sonja Woodall**[12], **Julie Arnold**[12], **Kathy Tucker**[13], **Michael Field**[14], **Sian Greening**[15], **Steve Gallinger**[16,17,18], **Melyssa Aronson**[18], **Renee Perrier**[19], **Michael O. Woods**[20], **Jane S. Green**[20], **Neal Walker**[21], **Christophe Rosty**[2,22], **Susan Parry**[12,23], and **Joanne P. Young**[2,3]

Corresponding Author: Associate Professor Joanne P. Young, Familial Cancer Laboratory, Queensland Institute of Medical Research, Herston Q4006, AUSTRALIA, Tel: +61 7 3362 0490, Fax: +61 7 3362 0108, Joanne.Young@qimr.edu.au.

*Authors contributed equally to the work.

The author acting as the submission's guarantor must be identified.
The author acting as the submission's guarantor is Joanne P. Young.

The authors must certify the role that each author had in conceiving, initiating and writing up the research project.

Author Contributions

Aung Ko Win - study concept and design; statistical analysis and interpretation of data; writing of the manuscript
Rhiannon J. Walters - data acquisition, interpretation of data; co-writing of manuscript
Daniel D. Buchanan - data acquisition and interpretation, critical review of manuscript
Mark A. Jenkins - study concept and design; statistical analysis and interpretation of results; critical review of manuscript
Kevin Sweet - ascertainment of cases, critical review of manuscript
Wendy L. Frankel - ascertainment of cases, critical review of manuscript
Albert de la Chapelle - ascertainment of cases, critical review of manuscript
Diane M. McKeone - ascertainment of cases, critical review of manuscript
Michael D. Walsh - histologist, data acquisition, critical review of manuscript
Mark Clendenning - data acquisition, critical review of manuscript
Sally-Ann Pearson - histologist, data acquisition, critical review of manuscript
Erika Pavluk - data acquisition and cleaning; preparation for analysis; critical review of manuscript
Belinda Nagler - data acquisition and cleaning; critical review of manuscript
John L. Hopper - genetic epidemiologist, ascertainment of cases, advice on analysis; critical review of manuscript
Michael R. Gattas - ascertainment of cases; critical review of manuscript
Jack Goldblatt - ascertainment of cases, critical review of manuscript
Jill George - ascertainment of cases, critical review of manuscript
Graeme K. Suthers - ascertainment of cases, critical review of manuscript
Kerry D. Phillips - ascertainment of cases, critical review of manuscript
Sonja Woodall - ascertainment of cases, critical review of manuscript
Julie Arnold - ascertainment of cases, critical review of manuscript
Kathy Tucker - ascertainment of cases, critical review of manuscript
Michael Field - ascertainment of cases, critical review of manuscript
Sian Greening - ascertainment of cases, critical review of manuscript
Steve Gallinger - ascertainment of cases, critical review of manuscript
Melyssa Aronson - ascertainment of cases, critical review of manuscript
Renee Perrier - ascertainment of cases, critical review of manuscript
Michael O. Woods - ascertainment of cases, critical review of manuscript
Jane S. Green - ascertainment of cases, critical review of manuscript
Neal Walker - pathologist, interpretation of data; critical review of manuscript
Christophe Rosty - pathologist, interpretation of data; critical review of manuscript
Susan Parry - ascertainment of cases, clinical interpretation, critical review of manuscript
Joanne P. Young - study concept and design, interpretation of data, writing of the manuscript

Identification of any relationships that any author or other entity that provided financial or editorial support may have in potential competing interests to those referenced in the submission.
No authors have competing interests.

[1]Centre for MEGA Epidemiology, School of Population Health, University of Melbourne, Carlton, VIC 3053, Australia [2]Familial Cancer Laboratory, Queensland Institute of Medical Research, Herston QLD 4006, Australia [3]School of Medicine, University of Queensland, Herston QLD 4006, Australia [4]Division of Human Genetics, Department of Internal Medicine, Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43221, USA [5]Department of Pathology, The Ohio State University, Columbus, OH 43221, USA [6]Human Cancer Genetics Program, Comprehensive Cancer Center, The Ohio State University, Columbus, OH 43221, USA [7]Queensland Clinical Genetics Service, Royal Childrens' Hospital, Herston Q4029, Australia [8]School of Paediatrics and Child Health, University of Western Australia, Nedlands, WA 6009, Australia [9]Genetic Services of Western Australia, Subiaco, WA 6008, Australia [10]Department of Paediatrics, University of Adelaide, SA 5005, Australia [11]South Australian Clinical Genetics Service, North Adelaide, SA 5009, Australia [12]New Zealand Familial Gastrointestinal Cancer Registry, Auckland City Hospital, Auckland, New Zealand [13]Hereditary Cancer Clinic, Prince of Wales Hospital, Randwick, NSW 2031, Australia [14]Department of Clinical Genetics, Royal North Shore Hospital, Sydney, NSW 2145, Australia [15]Illawarra Cancer Centre, Wollongong Hospital, Wollongong NSW, Australia [16]Cancer Care Ontario, Toronto, Ontario, Canada [17]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada [18]Zane Cohen Centre for Digestive Diseases, Mount Sinai Hospital, Toronto, Ontario, Canada [19]University of British Columbia and BC Cancer Agency, Vancouver, British Columbia, Canada [20]Discipline of Genetics, Memorial University of Newfoundland, St Johns, Newfoundland, Canada [21]Envoi Pathology, Herston, Q4006, Australia [22]Department of Molecular and Cellular Pathology, University of Queensland, Herston, Q4006, Australia [23]Department of Gastroenterology, Middlemore Hospital, Auckland, New Zealand

Abstract

OBJECTIVES—Serrated polyposis (hyperplastic polyposis) is characterized by multiple polyps with serrated architecture in the colorectum. While patients with serrated polyposis are known to be at increased risk of colorectal cancer (CRC) and possibly extracolonic cancers, cancer risk for their relatives has not been widely explored. The aim of this study was to estimate the risks of CRC and extracolonic cancers for relatives of patients with serrated polyposis.

METHODS—A cohort of the 1,639 first- and second-degree relatives of 100 index patients with serrated polyposis recruited regardless of a family history of polyps or cancer from genetic clinics in Australia, New Zealand, Canada and the USA, were retrospectively analysed to estimate the country-, age- and sex-specific standardized incidence ratios (SIRs) for relatives compared with the general population.

RESULTS—A total of 102 CRCs were observed in first- and second-relatives (SIR 2.25, 95% confidence interval, CI 1.75-2.93; $P<0.001$), with 54 in first-degree relatives (SIR 5.16, 95% CI 3.70-7.30; $P<0.001$) and 48 in second-degree relatives (SIR 1.38, 95% CI 1.01-1.91; $P=0.04$). Six pancreatic cancers were observed in first-degree relatives (SIR 3.64, 95% CI 1.70-9.21; $P=0.003$). There was no statistical evidence of increased risk for cancer of the stomach, brain, breast or prostate.

CONCLUSIONS—Our finding that relatives of serrated polyposis patients are at significantly increased risk of colorectal and pancreatic cancer, adds to the accumulating evidence that serrated polyposis has an inherited component.

Keywords

serrated polyposis; colorectal cancer; extracolonic cancers; hyperplastic polyposis

INTRODUCTION

Serrated polyposis, also known as hyperplastic polyposis, is a condition characterized by the presence of multiple epithelial polyps with serrated architecture in the colon and rectum (1). Patients with serrated polyposis are among the most difficult patient groups encountered in genetics clinics as they have no apparent causative germline mutation, and the phenotype is highly variable with a vast array of polyp numbers, sizes, and histological subtypes (2). Approximately 1 in 3000 individuals at age 55-64 years in the United Kingdom are thought to have serrated polyposis, and 50% of them have been identified to additionally have at least one conventional colorectal adenoma (3). These patients are at increased risk of early-onset colorectal cancer (CRC) (4-10) and possibly extracolonic cancers (11).

As reflected in the recently modified WHO clinical criteria (1), serrated polyposis likely encompasses a group of diseases, rather than a single disease, or a continuum, which is influenced by a variety of genetic and environmental modifiers. Although serrated polyposis has the hallmarks of a genetic disease (young-onset, multiplicity of polyps and cancers, and restricted ethnicity), an underlying genetic alteration has yet to be found. A family history of CRC has been reported for 33% to 59% of serrated polyposis patients (6, 12, 13), although other reports have suggested that this was a rare situation (14, 15). Boparai *et al* (16) estimated that the first-degree relatives of serrated polyposis patients had five times the incidence of CRC (standardized incidence ratio, SIR 5.4; 95% confidence interval, CI 3.7-7.8), which is a greater increased risk than for relatives of CRC cases, and 39 times the incidence of serrated polyposis (SIR 39; 95% CI 13-121) compared with the general population. Inherited CRC predisposition syndromes are, however, seldom confined to the colorectum. This can be seen in the autosomal dominantly inherited Lynch syndrome (17) and familial adenomatous polyposis (18) where increased risks of various extracolonic cancers are well reported.

The specific risk of extracolonic cancers for relatives of patients with serrated polyposis has not been reported, although extracolonic cancers have been noted in several previous publications (11, 19, 20). In this study, we have estimated the risks of CRC and extracolonic cancers for the first- and second-degree relatives of patients with serrated polyposis.

MATERIALS AND METHODS

Study Sample

We studied the first- and second-degree relatives of patients with multiple serrated polyps (more than 5) outside the rectum without a personal history of any cancer prior to diagnosis of serrated polyposis (index cases). Index cases were recruited between 2000 and 2010 from genetics clinics in Australia, New Zealand, Canada and the USA *regardless* of a family history of polyps or cancer, and represented the initial presentation in each family. All index cases diagnosed due to family screening, or carrying pathogenic mutations in mismatch repair genes or the *MUTYH* gene were excluded from the study. All index cases were referred to genetics clinics for hyperplastic polyposis (regardless of whether they had a personal or family history of CRC). Index cases were recruited by the Australasian Colorectal Cancer Family Registry (21), and the Genetics of Serrated Neoplasia study (http://www.qimr.edu.au/page/GSN/) to which Ohio State University Medical Center (USA), Familial Gastrointestinal Cancer Registry (Ontario, Canada), Memorial University of Newfoundland (Canada), the Genetics Clinics of Australia and the New Zealand Familial Gastrointestinal Cancer Registry have contributed (5, 12).

Attempts were made to contact (via the index case) and interview the relatives of index cases identified via the Australasian Colorectal Cancer Family Registry. Written informed

consents were obtained from all participants to take part in research and the study protocols were approved by local institutional research ethics review boards, as well as the Human Research Ethics Committee of the Queensland Institute of Medical Research (Protocols P628 and P912).

Data Collection

Information on demographics, personal characteristics, personal and family history of polyps, cancer, colonoscopic surveillance and surgery were obtained from index cases (and all participating relatives in some clinics) at time of recruitment. Reported cancer diagnoses and age at diagnosis were confirmed, where possible, using pathology reports or medical records. Pathology review of polyps was undertaken by a specialist gastrointestinal pathologist (CR or NIW) and information regarding the number, size, distribution, gross morphology, and histology of polyps was derived from the colonoscopy and histopathology reports. The total numbers of each polyp type were estimated during colonoscopy or from the surgical specimen if a colectomy was performed. Permission to access tumor tissue was obtained from participants.

To reduce the possibility of unintentionally including cases of metastatic cancer; cancers of lung, liver, bone and brain were only included if no other cancer was reported at or before the age of diagnosis.

Definitions

Serrated polyps were defined as any polyp with serrated crypt architecture (22) which includes both non-dysplastic polyps (hyperplastic polyp and sessile serrated adenoma/polyp) and dysplastic polyps (traditional serrated adenoma and sessile serrated adenoma/polyp with cytological dysplasia). Where polyp count was known, polyposis was categorized into two groups: those fulfilling WHO criterion-3 (>20 polyps throughout the colon) and those fulfilling WHO criterion-1 (>5 serrated polyps beyond the rectosigmoid with two exceeding 10 mm in diameter) (1). Depending on polyp count, where known, polyposis was also defined as moderate (5-79 polyps) or dense (≥80 polyps).

Statistical Analysis

Cancer-specific SIRs were calculated by dividing the observed numbers of cancers for the first- and second-degree relatives of patients with serrated polyposis by the expected numbers. The expected numbers of cancers were calculated by multiplying the age-, sex- and country-specific incidence for the general population with the corresponding observation time (person-years from birth) of the relatives. Age- and sex-specific cancer incidences in 1988-1992 for each country (Victorian Cancer Registry, Australia; National Cancer Registry, New Zealand; Ontario Cancer Registry, Canada; and the Surveillance, Epidemiology and End Results (SEER) registry, USA) were obtained from the International Agency for Research on Cancer (IARC) publication on Cancer Incidence in Five Continents (23). The period of 1988-1992 was selected for analysis because it was the closest available dataset to the mean calendar year of cancer diagnoses in the sample. The Jackknife method was used to estimate 95% confidence intervals (CIs) by allowing for any correlation of risk between relatives from the same family (24). Observation time for each subject started at birth and ended at the age at first diagnosis of cancer or last contact or death, whichever occurred first. For CRC, we censored each subject at the age of polypectomy except when it occurred within a year of the diagnosis of CRC (n=1). All index cases were excluded from the analysis.

Missing ages were estimated by use of a defined protocol. For relatives with missing ages at cancer diagnoses (31% of all cases), we assumed the age of diagnosis to be one year prior to

the last known age or, if last known age was not available, the median age at diagnosis of the specific cancer for the general population. The cancer-specific median age for each sex was obtained from the Queensland Cancer Registry for relatives from Australia and New Zealand (25), and SEER Cancer Statistics Review (1975-2000) for relatives from Canada and the USA (26). For unaffected relatives with missing ages at last contact (229 first- and 507 second-degree relatives), if an exact age was not known but an age range was provided, age was estimated as the midpoint of that range. In the absence of any age information, it was assumed that both parents of a common child were born in the same year, that a parent was aged 25 years at birth of a first child, and that there were two years between the births of children.

The SIRs of CRC for relatives were estimated stratified by the characteristics of polyps diagnosed in the index case: age at diagnosis (<50 and ≥50 years), nature of polyps (with or without adenocarcinoma), polyp distribution (proximal colon and pancolonic), and density of polyps (5-79 polyps and ≥80 polyps). All reported statistical tests were two-sided and $P<0.05$ was considered statistically significant. All these statistical analyses were done using Stata 11.0 (27).

Estimated cumulative risks (penetrance) of cancers to age 70 years and their 95% CIs for each sex were calculated by summing over sex-specific incidences $incidence_i$ at age i multiplied by the estimated SIR, based on the population incidences of Australia, using the formula:

$$1 - e^{-\sum_{i=0}^{age} SIR \cdot incidence_i}$$

RESULTS

A total of 120 cases were recruited *regardless* of a family history of colorectal polyps or cancer. Of these, 20 cases were excluded because 14 were diagnosed due to family screening, 5 carried mismatch repair gene mutations and 1 carried a biallelic *MUTYH* mutation. The remaining 100 cases (33 were recruited from Australia, 41 from New Zealand, 6 from Canada and 20 from the USA) had 609 first-degree relatives (316 females) and 1,030 second-degree relatives (488 females) contributing data for this analysis (Table 1).

Of the 100 index cases (63% female), minimum polyp counts were available from 66 (66%) of whom all but 7 met WHO criterion-3 (>20 serrated polyps throughout the colon). Of the 84 index cases whose location of polyps was known, 81 (96%) had pancolonic polyposis and three (4%) had polyposis concentrated in the proximal colon. Thirty-one of the 100 index cases had CRC (31%) and 17 of these (55%) were located in the proximal colon. Three proximal CRCs were multiple synchronous cancers. Average age at diagnosis was 48 (standard deviation, SD 15) years and average minimal polyp number observed in index cases was 45 (SD 32) (Table 2). Sessile serrated adenomas were described in 32/64 females (50%) and 11/36 males (31%). Details of each case are available in Supplementary Table 1.

We observed a total of 102 CRCs in the first- and second-degree relatives combined (SIR 2.25, 95% CI 1.75-2.93; $P<0.001$), with 54 in first-degree relatives (SIR 5.16, 95% CI 3.70-7.30; $P<0.001$) and 48 in second-degree relatives (SIR 1.38, 95% CI 1.01-1.91; $P=0.04$) (Table 3). The risk of CRC for relatives was relatively greater when the index case was diagnosed under age 50 compared with when the index case was diagnosed at age 50 and above, but this did not reach statistical significance ($P=0.07$). There was no statistical evidence for difference in risks of CRC for relatives when numbers of polyps diagnosed in

the index case were considered (see Table 4). The median age at which CRC developed in first-degree relatives was 55 years and in second-degree relatives was 66 years. The average age at diagnosis of CRC in either the first- or second-degree relatives of patients with serrated polyposis diagnosed under and over the age of 50 years was not significantly different (P=0.97).

A total of 11 pancreatic cancers were observed in this study cohort in which six cases were in first-degree relatives (SIR 3.64, 95% CI 1.70-9.21; P=0.003). We observed no evidence of an increased risk for cancer of the stomach, brain, prostate or female breast cancer. Cancers of other organs were observed in the cohort as follows: kidney (n=3), urinary bladder (n=5), leukemia (n=5), lymphoma (n=5), myeloma (n=2), bone (n=3), thyroid (n=2), oesophagus (n=5), liver (n=5), biliary tract (n=1), endometrium (n=3), ovary (n=4), cervix (n=4) and testis (n=1).

Table 5 shows the estimated cancer-specific cumulative risk (penetrance) for first- and second-degree relatives of patients with serrated polyposis. The estimated cumulative risks to age 70 years for the first-degree relatives were: for CRC, 15% (95% CI 11-21%) for men and 12% (95% CI 8-16%) for women and for pancreatic cancer, 2% (95% CI 1-6%) for men and 1.5% (95% CI 0.7-4%) for women. When the index case was diagnosed under age 50, the cumulative risk of CRC for first-degree relatives was 24% (95% CI 15-39%) for men and 19% (95% CI 11-30%) for women. When the index case was diagnosed at age 50 and above, the cumulative risk of CRC for first-degree relatives was 13% (95% CI 9-20%) for men and 10% (95% CI 7-15%) for women.

DISCUSSION

First- and second-degree relatives of patients with serrated polyposis had a significantly increased risk of developing CRC. In addition, first-degree relatives demonstrated a significantly increased risk of pancreatic cancer. Together these findings support an inherited component for serrated polyposis. Though increased risks for first-degree relatives could be due to shared environment, the observation that the CRC risk extended to second-degree relatives, and that relatives were also at increased risk for extracolonic cancers, increases the likelihood of a genetic aetiology for serrated polyposis (28). Our estimate of CRC risk for first-degree relatives did not differ significantly from the relative risk estimated by Boparai *et al* (16) (P=0.86).

Extracolonic cancers in relatives of a *BRAF*-mutated CRC proband (implying origin in a serrated polyp) were first described in a Swedish study of familial CRC in 2006 (20), and further extracolonic associations were seen in a Canadian study (29). A single anecdotal report (19), and a clinical description (11) reported occurrence of extracolonic cancers in serrated polyposis patients and their relatives. However, until our study, the magnitude of extracolonic cancer risk for relatives had not been estimated. A range of extracolonic cancers were observed in the study cohort but the cancer-specific numbers were too low to determine with any degree of certainty whether they occurred more often than expected. Common cancers such as those of the breast lung and prostate were not increased above what would be expected in the population. An apparent decreased risk for lung cancer was observed in second-degree relatives. We have no explanation for this association, however it may be a consequence of our analysis excluding any second cancers within one year of the first cancer diagnosis, which was done to minimise inclusion of metastatic disease.

We observed a significantly increased risk of pancreatic cancer for first-degree relatives of patients with serrated polyposis which is a novel finding. No cases of pancreatic cancer were seen in the serrated polyposis cases themselves, although given the young average age at

diagnosis of polyposis (48 years), this is not unexpected. Pancreatic cancer occurs in familial cancer syndromes such as Peutz-Jeghers syndrome (30), and Familial Atypical Multiple Mole Melanoma syndrome (31) where its risk ranges from 9 to132-fold that of the population. It also occurs in familial pancreatitis, with a relative risk of 50-80 fold, and in families with mutations in *BRCA2* and its binding partner *PALB2*, where the risk varies from 3.5-10 fold that of the population (32). Our estimate for pancreatic cancer risk in serrated polyposis at 3.64 is commensurate with the lower estimates for *BRCA2* families. In population terms, the pancreas is less likely to develop a malignancy than any other organ in the gastrointestinal tract, with the exception of the small intestine (32). Pancreatic cancer is highly age-dependent, and occurs in the population around 70 yrs of age (33, 34). The median age at diagnosis for pancreatic cancer in our study was 73 years, not indicative of an early-age of onset. Rather, the increased frequency is suggestive of an enhanced response to risk factors such as smoking, obesity, and diabetes (34), factors which are also associated with the development of serrated polyps (35). Pancreatic cancer is difficult to prevent and there are currently no robust screening tests for early detection. Endoscopic ultrasound has been trialed in very high-risk families and has shown some promise in the detection of early precursor lesions in asymptomatic individuals (36).

Biological explanations for the association between serrated polyposis and extracolonic cancers are not known, however, our findings support the hypothesis that this condition represents an inherited cancer predisposition in which the phenotype is most strongly expressed in the colorectum. It is also possible that environmental triggers may be interacting with the genetic predisposition to produce both colonic and extracolonic cancers. Finally, more than one condition may be segregating in these families. Jarrar *et al* (19) reported that seven of 651 families who met the criteria of Amsterdam I, Amsterdam II, Amsterdam-like, or familial colorectal cancer, had a high prevalence of serrated polyps. One of the scenarios raised in that report was a co-occurrence of two cancer pathways; Lynch syndrome serrated polyposis. However our findings suggest that the extracolonic cancers and at least, observed in relatives of serrated polyposis patients, are unlikely to be due to co-occurring Lynch syndrome mutations as index cases with a mismatch repair gene mutation were excluded from the study.

Serrated polyposis as currently defined is likely to comprise a heterogeneous group of conditions. The pattern of inheritance in at least some serrated polyposis patients may be consistent with a recessive mode (37), analagous to *MUTYH*-associated polyposis (MAP) caused by germline mutations in the *MUTYH* gene. Increased risks of cancer for relatives of patients with MAP have been found for CRC, duodenal, ovary, bladder and skin cancer for biallelic mutation carriers (38). Moreover, an increased risk of CRC, gastric and endometrial cancer has been reported for monoallelic mutation carriers (39). Until a genetic cause is identified for serrated polyposis, studies will continue to be based on a clinical definition.

The strengths of this study are 1) that it was based, to our knowledge, on the largest sample to date of relatives of index patients with serrated polyposis; 2) it is the first study to quantify the risks of extracolonic cancers for relatives of patients with serrated polyposis; 3) index cases were *not* ascertained because of a previous family history of polyps or cancer and therefore the estimates from this study are less likely to be inflated due to ascertainment bias (40); and 4) we accounted for familial correlation in the risk of cancer to derive appropriate measure of estimate imprecision.

Our study has several limitations including the presence of unverified cancers, unaccounted for time and geographic variation. These might increase the imprecision of estimates more than indicated by the reported confidence intervals. Estimates from this study should be generalizable to relatives of symptomatic patients with serrated polyposis identified in a

clinical setting. As all index cases were recruited from genetics clinics, this raises the possibility that relatives of symptomatic patients may represent a more aggressive phenotype associated with a higher 'familial risk profile' compared with other asymptomatic patients. However, symptoms such as abdominal pain or change in bowel habit which first brought the index patients to their primary care clinician are also very common outside the setting of serrated polyposis, and may have had nothing to do with their serrated polyposis condition (41, 42). Therefore it is not possible to state at this time that an aggressive phenotype should be inferred. A further limitation of the study is that it is not possible to know whether an endoscopist referred the patient to a genetics clinic because of polyp burden or because of family history. As the family history data used in this study were determined using genetics clinic pedigree records, we do not know the extent of family history recorded by the endoscopists. However, it has been observed that even in high-risk patients diagnosed under age 50, family history was not noted in 49-83% of cases (43, 44).

Our findings suggest that relatives of patients with serrated polyposis could benefit from appropriate colonoscopic surveillance. Current practice for first-degree relatives is usually five-yearly colonoscopy from the age of 40-50 years or from an age 5 years younger than the age at which serrated polyposis was diagnosed in the family. The median age at which CRC was diagnosed in first-degree relatives in our study (55 years old) supports these guidelines for surveillance. Further independent studies are required to confirm the risks of extracolonic cancers for relatives of patients with serrated polyposis. Also, given the arbitrary nature of the current criteria for the identification of serrated polyposis (1) and the initial observation of extracolonic cancers in relatives of index cases whose CRC arose from a serrated polyp (20), the implications of this finding may be applicable beyond the stringent criteria for diagnosis of serrated polyposis, identifying some families with both CRC and pancreatic cancer (in which Lynch syndrome is excluded) as having a serrated neoplasia predisposition.

This large, international study has observed that relatives of serrated polyposis patients are at significantly increased risks of colorectal and pancreatic cancer. These findings add to the accumulating evidence that serrated polyposis has an inherited component, whilst also highlighting the need for surveillance in relatives of patients with serrated polyposis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of all financial and, if relevant, any editorial assistance received to support the research project and/or preparation of the article.

This work was supported by grants from the Cancer Council Queensland, the Hicks Foundation in Victoria, and the National Cancer Institute, National Institutes of Health under 1R01CA123010 (Genetics of Serrated Neoplasia) and RFA # CA-95-011 and through cooperative agreements with the Australasian Colorectal Cancer Family Registry (U01 CA097735). This work was supported in part by the National Cancer Institute (CA67941 and CA16058). JPY is a Cancer Council Queensland Senior Research Fellow. CR is the Jass Pathology Fellow (2010-2011). The authors acknowledge the contribution of staff and participants in the Australasian Colorectal Cancer Family Registry, the Genetics of Serrated Neoplasia (GSN) study, the New Zealand Familial Gastrointestinal Cancer Registry, the Ohio State University Medical Center (USA), Familial Gastrointestinal Cancer Registry (Canada), Memorial University of Newfoundland (Canada) and The Jeremy Jass Memorial Pathology Collection.

REFERENCES

1. Snover, D.; Ahnen, D.; Burt, R., et al. WHO Classification of Tumours of the Digestive System. Fourth Edition. IARC; 2010. Serrated polyps of the colon and rectum and serrated polyposis.

2. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology. 1996; 110:748–55. [PubMed: 8608884]
3. Lockett M, Atkin W. Hyperplastic polyposis: prevalence and cancer risk. Gut. 2010; 48:A4.
4. Boparai KS, Mathus-Vliegen EM, Koornstra JJ, et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. Gut. 2010; 59:1094–100. [PubMed: 19710031]
5. Buchanan DD, Sweet K, Drini M, et al. Risk factors for colorectal cancer in patients with multiple serrated polyps: a cross-sectional case series from genetics clinics. PLoS ONE. 2010; 5:e11636. [PubMed: 20661287]
6. Carvajal-Carmona LG, Howarth KM, Lockett M, et al. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. J Pathol. 2007; 212:378–85. [PubMed: 17503413]
7. Hyman NH, Anderson P, Blasyk H. Hyperplastic polyposis and the risk of colorectal cancer. Dis Colon Rectum. 2004; 47:2101–4. [PubMed: 15657661]
8. Lage P, Cravo M, Sousa R, et al. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. Am J Gastroenterol. 2004; 99:1779–84. [PubMed: 15330918]
9. Leggett BA, Devereaux B, Biden K, et al. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol. 2001; 25:177–84. [PubMed: 11176066]
10. Yeoman A, Young J, Arnold J, et al. Hyperplastic polyposis in the New Zealand population: a condition associated with increased colorectal cancer risk and European ancestry. N Z Med J. 2007; 120:U2827. [PubMed: 18264196]
11. Kalady MF, Jarrar A, Leach B, et al. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. Dis Colon Rectum. 2011; 54:164–70. [PubMed: 21228663]
12. Buchanan DD, Sweet K, Drini M, et al. Phenotypic diversity in patients with multiple serrated polyps: a genetics clinic study. Int J Colorectal Dis. 2010; 25:703–12. [PubMed: 20213458]
13. Chow E, Lipton L, Lynch E, et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. Gastroenterology. 2006; 131:30–9. [PubMed: 16831587]
14. Ferrandez A, Samowitz W, DiSario JA, et al. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. Am J Gastroenterol. 2004; 99:2012–8. [PubMed: 15447765]
15. Williams GT, Arthur JF, Bussey HJ, et al. Metaplastic polyps and polyposis of the colorectum. Histopathology. 1980; 4:155–70. [PubMed: 7358345]
16. Boparai KS, Reitsma JB, Lemmens V, et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. Gut. 2010; 59:1222–1225. [PubMed: 20584785]
17. Vasen HFA. Clinical Diagnosis and Management of Hereditary Colorectal Cancer Syndromes. J Clin Oncol. 2000; 18:81s–92. [PubMed: 11060333]
18. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. Hum Mol Genet. 2001; 10:721–733. [PubMed: 11257105]
19. Jarrar AM, Church JM, Fay S, et al. Is the phenotype mixed or mistaken? Hereditary nonpolyposis colorectal cancer and hyperplastic polyposis syndrome. Dis Colon Rectum. 2009; 52:1949–55. [PubMed: 19934914]
20. Vandrovcova J, Lagerstedt-Robinsson K, Pahlman L, et al. Somatic BRAF-V600E Mutations in Familial Colorectal Cancer. Cancer Epidemiol Biomarkers Prev. 2006; 15:2270–3. [PubMed: 17119056]
21. Newcomb PA, Baron J, Cotterchio M, et al. Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev. 2007; 16:2331–2343. [PubMed: 17982118]
22. Jass JR. Serrated adenoma of the colorectum and the DNA-methylator phenotype. Nat Clin Pract Oncol. 2005; 2:398–405. [PubMed: 16130936]
23. Parkin, DM.; Whelan, SL.; Ferlay, J., et al., editors. Cancer Incidence in Five Continents. Vol. VII. IARC; Lyon, France: 1997.
24. Gould W. Jackknife estimation. Stata Technical Bulletin. 1995; 4:25–29.

25. Baade, P.; Coory, M.; Ring, I. National Health Priority Cancers in Queensland (1982 to 1997). Health Information Centre, Queensland Cancer Registry; Brisbane: 2000.
26. Ries, L.; Eisner, M.; Kosary, C., et al., editors. SEER Cancer Statistics Review, 1975-2000. National Cancer Institute; Bethesda, MD: 2003.
27. Stata Statistical Software: Release 11. StataCorp LP; College Station, TX: 2009.
28. Maul JS, Burt RW, Cannon-Albright LA. A familial component to human rectal cancer, independent of colon cancer risk. Clin Gastroenterol Hepatol. 2007; 5:1080–4. [PubMed: 17625976]
29. Wish T, Hyde A, Parfrey P, et al. Increased Cancer Predisposition in Family Members of Colorectal Cancer Patients Harboring the p. V600E BRAF Mutation: a Population-Based Study. Cancer Epidemiol Biomarkers Prev. 2010; 19:1831–9. [PubMed: 20570909]
30. van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010; 105:1258–64. author reply 1265. [PubMed: 20051941]
31. Lynch HT, Fusaro RM, Lynch JF, et al. Pancreatic cancer and the FAMMM syndrome. Fam Cancer. 2008; 7:103–12. [PubMed: 17992582]
32. Hruban RH, Canto MI, Goggins M, et al. Update on familial pancreatic cancer. Adv Surg. 2010; 44:293–311. [PubMed: 20919528]
33. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst. 2010; 102:119–26. [PubMed: 20068195]
34. Maisonneuve P, Lowenfels AB. Epidemiology of pancreatic cancer: an update. Dig Dis. 2010; 28:645–56. [PubMed: 21088417]
35. Anderson JC, Rangasamy P, Rustagi T, et al. Risk factors for sessile serrated adenomas. J Clin Gastroenterol. 2011; 45:694–9. [PubMed: 21325950]
36. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol. 2004; 2:606–21. [PubMed: 15224285]
37. Young J, Jenkins M, Parry S, et al. Serrated pathway colorectal cancer in the population: genetic consideration. Gut. 2007; 56:1453–1459. [PubMed: 17566021]
38. Vogt S, Jones N, Christian D, et al. Expanded Extracolonic Tumor Spectrum in MUTYH-Associated Polyposis. Gastroenterology. 2009; 137:1976–1985.e10. [PubMed: 19732775]
39. Win AK, Cleary SP, Dowty JG, et al. Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. Int J Cancer. 2011; 129:2256–2262. [PubMed: 21171015]
40. Win AK, Hopper JL, Jenkins MA. Estimates of familial risks from family data are biased when ascertainment of families is not independent of family history. Gut. 2011; 60:1162–1163. [PubMed: 20966021]
41. Adelstein BA, Irwig L, Macaskill P, et al. Who needs colonoscopy to identify colorectal cancer? Bowel symptoms do not add substantially to age and other medical history. Aliment Pharmacol Ther. 2010; 32:270–81. [PubMed: 20456307]
42. Adelstein BA, Macaskill P, Chan SF, et al. Most bowel cancer symptoms do not indicate colorectal cancer and polyps: a systematic review. BMC Gastroenterol. 2011; 11:65. [PubMed: 21624112]
43. Foo W, Young JM, Solomon MJ, et al. Family history? The forgotten question in high-risk colorectal cancer patients. Colorectal Dis. 2009; 11:450–5. [PubMed: 19508517]
44. Perea J, Ortiz M, Hidalgo M, et al. Importance of family history in colorectal cancer clinical practice. Colorectal Dis. 2010; 12:606. [PubMed: 20105203]

WHAT IS CURRENT KNOWLEDGE?

- Patients with serrated polyposis are at increased risk of early-onset colorectal cancer (CRC) and possibly extracolonic cancers.
- Risk of colorectal and extracolonic cancers for relatives of patients with serrated polyposis has not been explored extensively.

WHAT IS NEW HERE?

Both first- and second-degree relatives of index serrated polyposis patients are at increased risk of CRC.

First-degree relatives of patients with serrated polyposis are at significantly increased risk of pancreatic cancer.

This finding adds to the accumulating evidence that serrated polyposis has an inherited component.

Relatives of patients with serrated polyposis could benefit from appropriate colonoscopic surveillance.

Table 1

Baseline characteristics of relatives of index cases with serrated polyposis

Country	Total index cases No (%)	First-degree relatives No (%)	Second-degree relatives No (%)	Combined No (%)
Australia	33 (33)	205 (33)	352 (34)	557 (34)
New Zealand	41 (41)	230 (38)	341 (33)	571 (35)
Canada	6 (6)	42 (7)	81 (8)	123 (7)
USA	20 (20)	132 (22)	256 (25)	388 (24)
Total	100	609	1,030	1,639

Table 2

Baseline characteristics of index cases with serrated polyposis

		Number	%
Sex			
	Male	37	37
	Female	63	63
Serrated polyposis			
	Yes	64	64
	Suspected	36	36
WHO criterion			
	1	7	11
	3	59	89
	unknown	34	
Density of polyps			
	Moderate (5–79 polyps)	54	82
	Dense (≥80 polyps)	12	18
	unknown	34	
Distribution of polyps			
	pancolonic	81	96
	concentrated in the proximal colon	3	4
	unknown	16	
Adenocarcinoma			
	absent	69	69
	present	31	31
Adenoma			
	absent	15	22
	present	54	78
	unknown	31	
		Mean	SD
Age at diagnosis		47.8	15.0
Minimal polyp count		45	32
Maximum dimension of polyp (mm)		13.3	7.7

Table 3

Cancer-specific standardized incidence ratios (SIRs) for first- and second-degree relatives of patients with serrated polyposis compared with the general population

	Combined					First-degree relatives					Second-degree relatives				
	Median age (min–max)	**O**	**E**	**SIR (95% CI)**	***P***	**Median age (min–max)**	**O**	**E**	**SIR (95% CI)**	***P***	**Median age (min–max)**	**O**	**E**	**SIR (95% CI)**	***P***
Both sexes															
Colorectal cancer	60 (25–85)	102	45.25	2.25 (1.75–2.93)	<0.001	55 (25–83)	54	10.47	5.16 (3.70–7.30)	<0.001	66 (34–85)	48	34.78	1.38 (1.01–1.91)	0.04
Pancreatic cancer	75 (45–90)	11	6.93	1.59 (0.87–3.19)	0.16	73 (45–87)	6	1.65	3.64 (1.70–9.21)	0.003	75 (47–90)	5	5.28	0.95 (0.40–2.78)	0.92
Gastric cancer	71 (51–80)	10	7.81	1.28 (0.68–2.72)	0.49	67 (51–69)	3	1.95	1.54 (0.48–7.47)	0.53	75 (55–80)	7	5.87	1.19 (0.59–2.78)	0.66
Brain cancer	57 (7–64)	8	6.21	1.29 (0.62–3.17)	0.54	58 (56–59)	2	1.77	1.13 (0.25–10.98)	0.90	57 (7–64)	6	4.45	1.35 (0.64–3.40)	0.48
Lung cancer	68 (34–83)	24	43.37	0.55 (0.36–0.87)	0.01	59 (34–83)	9	10.36	0.87 (0.37–2.47)	0.77	68 (45–82)	15	33.00	0.45 (0.28–0.77)	0.002
Female															
Breast cancer	59 (25–87)	41	41.71	0.98 (0.67–1.48)	0.92	55 (25–85)	15	10.46	1.43 (0.86–2.56)	0.20	59 (34–87)	26	31.25	0.83 (0.53–1.36)	0.43
Male															
Prostate cancer	72 (50–86)	21	32.50	0.65 (0.42–1.03)	0.06	70 (62–75)	5	7.53	0.66 (0.29–1.87)	0.38	72 (50–86)	16	24.96	0.64 (0.38–1.15)	0.11

O = observed number of cancers, E = Expected number of cancers

Table 4

Standardized incidence ratios (SIRs) of colorectal cancer (CRC) for first- and second-degree relatives stratified by the characteristics of polyps diagnosed in patients with serrated polyposis

Characteristics of polyps in index case	Combined				First-degree relatives				Second-degree relatives			
	Median age (min–max)	O*	E	SIR (95% CI)	Median age (min–max)	O*	E	SIR (95% CI)	Median age (min–max)	O*	E	SIR (95% CI)
Age of onset												
<50 years	60 (27–80)	44	14.53	3.03 (2.12–4.40)	51 (27–80)	18	2.22	8.11 (4.71–14.35)	65 (34–80)	26	12.31	2.11 (1.40–3.26)
≥50 years	60 (25–85)	58	30.72	1.89 (1.34–2.73)	56 (25–83)	36	8.25	4.31 (2.88–6.82)	70 (36–85)	22	22.47	0.98 (0.61–1.64)
P for difference				0.07				0.08				0.02
Nature of polyps												
Without adenocarcinoma	59 (25–85)	79	28.94	2.73 (2.05–3.68)	55 (25–83)	43	6.63	6.48 (4.38–9.74)	66 (36–85)	36	22.31	1.61 (1.14–2.33)
With adenocarcinoma	60 (27–80)	23	16.30	1.23 (0.88–2.33)	60 (27–80)	11	3.83	2.87 (1.55–5.79)	64 (34–75)	12	12.47	0.96 (0.50–2.04)
P for difference				0.01				0.04				0.20
Location												
Proximal colon	54 (43–82)	5	1.82	2.75 (1.71–4.43)	63 (43–82)	2	0.41	4.87 (2.11–13.11)	54 (43–80)	3	1.41	2.13 (1.10–3.76)
Pancolonic	61 (25–85)	76	36.95	2.06 (1.53–2.80)	55 (25–83)	38	8.87	4.29 (2.88–6.54)	66 (34–85)	38	28.08	1.35 (0.95–1.98)
P for difference				0.32				0.80				0.21
Density of polyps												
Moderate (5–79 polyps)	60 (25–85)	56	25.21	2.22 (1.58–3.19)	55 (25–83)	29	5.32	5.45 (3.41–9.08)	66 (36–85)	27	19.89	1.36 (0.92–2.05)
Dense (≥80 polyps)	58 (27–62)	8	4.47	1.79 (0.87–4.02)	47 (27–62)	4	1.30	3.07 (1.69–6.44)	58 (34–60)	4	3.17	1.26 (0.37–6.29)
P for difference				0.62				0.18				0.92

O = observed number of CRC, E = Expected number of CRC

* The summation of these numbers may not be the same with the total of CRC observed in first- and second-degree relatives because of missing data on polyp characteristics (age of onset, location, minimum polyp counts).

Table 5

Cumulative risk % of different cancers to age 70 years for first- and second-degree relatives of patients with serrated polyposis

		Cumulative risk % (95% confidence interval)		
		Combined	**First-degree relatives**	**Second-degree relatives**
Colorectal cancer				
	Male	7.01 (5.49–9.02)	15.34 (11.26–20.99)	4.36 (3.21–5.98)
	Female	5.23(4.10–6.76)	11.60 (8.46–16.01)	3.24 (2.38–4.46)
Pancreatic cancer				
	Male	0.99 (0.54–1.97)	2.25 (1.06–5.59)	0.59 (0.25–1.72)
	Female	0.66 (0.36–1.32)	1.50 (0.70–3.75)	0.39 (0.17–1.15)