COLORECTAL CANCER

Risk of colorectal cancer in juvenile polyposis

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Background: Juvenile polyposis (JP) is an autosomal-dominant syndrome characterised by the development of hamartomatous gastrointestinal polyps and is associated with colorectal cancer. However, the relative and absolute risk of colorectal malignancy in these patients is not known.
Methods: The incidence rates of colorectal cancer in patients with JP were compared with that of the general population through person-year analysis with adjustment for demographics.
Results: In patients with JP, the RR (95% CI) of colorectal cancer was 34.0 (14.4 to 65.7). Similar risks were noted in both males (30.0, 9.6 to 68.6) and females (43.7, 8.8 to 125). The cumulative life-time risk for colorectal cancer was 38.7%. The mean (SD) age of diagnosis of colorectal cancer was 43.9 (10.4) years. Other gastrointestinal malignancies were not noted in this cohort.
Conclusion: Patients with JP have a markedly increased RR and absolute risk for colorectal cancer and require vigilant colorectal surveillance starting at young age. A low threshold for recommending surgery with consideration for removal of the entire colorectum seems warranted.

Juvenile polyposis (JP) is an autosomal-dominant syndrome characterised by the development of histopathological juvenile polyps in the gastrointestinal tract. Polyps usually occur by the third decade of life and primarily affect the colorectum.[1] Recently, investigators have discovered that germline mutations in the *BMPR1A* and *SMAD4/MADH4* gene cause this disorder in a minority (39%) of patients.[2] Also, mutation of the *ENG* gene may[3] or may not be[4] a cause of early-onset JP.

JP has been associated with increased risk of colorectal cancer. Evidence for this concept comes from a limited number of case series and collections of literature case reports, which provide variable estimates of the risk of colorectal cancer.[5–12] Also, other malignancies, including gastric, small bowel and pancreatic cancer, have been noted in some studies. However, a formal risk assessment of gastrointestinal cancer in patients with JP has not been reported.

The purpose of this study was to define the magnitude of risk for colorectal cancer in patients with JP. The occurrence of colorectal cancer in patients with JP from The Johns Hopkins Polyposis Registry and Clinic, The Johns Hopkins Hospital, Baltimore, Maryland, USA, were compared with the general population of the US through person-year analysis.

METHODS

Patient data were collected from The Johns Hopkins Polyposis Registry and clinic. Patients were defined as having JP according to the following accepted clinical criteria[1 5]: (1) at least five juvenile polyps in the colorectum, (2) juvenile polyps throughout the gastrointestinal tract or (3) any number of juvenile polyps in a person with a known family history of juvenile polyps. This study was approved by the Johns Hopkins Joint Committee on Clinical Investigation (institutional review board).

A risk assessment for colorectal adenocarcinoma was performed. Computation of person-years at risk for colorectal cancer started on 1 January 1970 and lasted until 1 July 2005. Patients were considered to be at risk from birth until date of diagnosis of colorectal cancer, the date of death or the closing date of the study. Patients were censored at age 85 years.

Person-years at risk were calculated for ages 0–84 years according to sex, race and age-specific categories during the subsequent 5-years calendar time period of observation using a computer program for cohort analysis.[13] Expected colorectal cancer cases were calculated by multiplying the number of person-years for each of 5-year age groups and sex by the corresponding race-, age-, sex- and calendar time-specific incidence rate for the general US population. The Surveillance, Epidemiology and End Results data for the US population were used[14] utilising 5-year calendar time periods as conventionally provided by this dataset. The ratio of observed carcinomas to the expected number was computed with a test of significance and 95% CIs assuming a Poisson distribution. This ratio forms the relative risk (RR) and compares cancer risk of the study population with that of the general population. Using the absolute rates for each 5-year age group, the cumulative risk was calculated using the formula: cumulative risk = 1−exp (−cumulative rate).[13]

RESULTS

The study population for the person-year analysis consisted of 84 patients with JP from 44 pedigrees contributing 1652.2

Table 1 Patients with juvenile polyposis who developed colorectal cancer

Age at diagnosis of colorectal cancer (years)	Sex	Race	Prior partial colectomy (age in years)	Death from colorectal cancer
30	F	W	No	No
32	F	W	Yes (28)	No
37	M	W	Yes (18)	Yes
41	M	W	No	Yes
48	F	W	No	No
52	M	W	Yes (19)	Yes
53	M	W	No	Yes
58	M	W	No	Yes

F, female; M, male; W, white.

Abbreviation: JP, juvenile polyposis

Table 2 Risk analysis of colorectal cancer in patients with juvenile polyposis as compared with the general population of the US (The Surveillance, Epidemiology and End Results data)

Group	Person-years	Numbers of colorectal cancers	RR (observed/expected)	95% CI	Rate per 100 000 (person-years)
Males	738.9	5	30.0	9.6 to 68.6	676.7
Females	913.3	3	43.7	8.8 to 125.0	328.5
Combined	1652.2	8	34.0	14.4 to 65.7	484.2

person-years of follow-up. This included 35 white and 7 black males (738.9 person-years of follow-up), and 39 white and 3 black females (913.3 person-years of follow-up).

Table 1 lists the patients with JP having colorectal adenocarcinoma. The mean (SD) age of diagnosis of colorectal cancer was 43.9 (10.4) years. Two patients with prior prophylactic colectomy with ileoanal anastomosis and one with colectomy and Hartman's pouch developed subsequent cancer in the retained rectum. In all, 5 of 8 (63%) patients with colorectal cancer died of this malignancy. No cases of oesophageal, gastric, small bowel or pancreatic cancer were noted in this cohort.

Table 2 shows the results of the person-year analysis for colorectal cancer. The RR (95% CI) for colorectal cancer in patients with JP was 34.0 (14.4 to 65.7). This significantly increased risk was similar in males (30.0, 9.6 to 68.6) and females (43.7, 8.8 to 125). On the basis of an 80-year life span, the absolute risk for colorectal cancer was 38.7 per 100 persons.

DISCUSSION

In this study performed by person-year analysis, both male and female patients with JP had a significantly elevated RR (34.0) of colorectal cancer compared with the general population. The life-time risk of colorectal cancer was calculated at 39%. These findings are consistent with several case series,[5 6 8–12] and a publication that compiled literature reports,[7] estimating a 13–38% frequency of colorectal cancer in patients with JP. Jass[15] reported a 68% cumulative risk of colorectal cancer in patients from the St Mark's Registry but details were not provided.

In JP, as in the other inherited syndromes of colorectal neoplasia, increased risk of colon malignancy seems to be associated with a younger age of diagnosis. In this study, the mean age of colorectal cancer diagnosis was 43.9 years with one case being diagnosed at age 30 years. In two previous reports, the mean age of colorectal cancer diagnosis was 34 years with one individual being diagnosed early at age 15 years.

Extracolonic gastrointestinal cancers (<30 confirmed literature cases) have been reported in other studies of patients with JP. These have included stomach, small bowel and pancreatic cancers.[8 9 11 12] None of the patients in our cohort had these malignancies, and consequently, formal risk analysis for these tumours could not be performed. Evaluation of literature reports shows gastric and small bowel tumours, occurring together at about one-fifth the frequency of colorectal cancers in this patient group.

A caution raised by comparison of a registry-based population to the general US population is detection bias—that is, surveillance of the population in the registry may lead to higher diagnosis of certain disorders compared with the general population. Although this concern cannot be discounted, none of the patients with malignancy came to the attention of the registry as being secondary to the diagnosis of colorectal cancer. Also, the risks generated for colorectal cancer in patients with JP in this analysis are consistent with the prevailing literature. Moreover, our estimates of colorectal cancer risk are probably conservative, as patients with partial colectomy were not censored from the analysis at the time of surgery. In this regard, three of the patients with colorectal cancer developed malignancy in the retained rectum several years after the partial colectomy. Finally, marked risk of colorectal neoplasia is also noted in a transgenic mouse model of JP produced by inhibition of bone morphogenetic protein signalling. In these animals, intestinal epithelial neoplasia and disruption of the Wnt pathway were noted in a majority of mice.[16]

In summary, this study, taken together with other literature data, argues for a markedly increased risk of colorectal cancer in patients with JP. These findings are in concert with expert opinion, which recommends the commencement of screening for JP in at-risk individuals at age 15 years (or earlier if the patient is having symptoms).[17 18] Screening with genetic testing is preferable, but if not feasible, colonoscopy at an interval of every 3 years is advised. Surveillance of affected individuals is advocated at least biennially by colonoscopy initiated by age 15 years.[17] Also, others advise periodic upper endoscopy and evaluation of the small intestine.[17] Based on colorectal cancer risk estimates, a low threshold for recommending colectomy (ie, when colorectal dysplasia is present or adequate surveillance is not possible) with consideration for removal of the entire colorectum seems warranted.

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EDITOR'S QUIZ: GI SNAPSHOT

An unusual cause of gastric outlet obstruction

Robert Spiller, *Editor*

Clinical presentation

A 55-year-old woman presented with a 1-day history of repeated vomiting of non-bile stained content. She also had intermittent epigastric pain and dizziness for 3 months. She did not have a history of tarry stool or fresh per rectal bleeding. She was pale and abdominal examination showed succession splash and a ballotable right upper quadrant mass. Laboratory tests revealed a haemoglobin level of 4.7 g/dl and an albumin level of 27 g/l. CT of the abdomen was performed (fig 1 A–C).

Question

What is the most likely diagnosis? What are the possible treatments?

See page 1018 for answer

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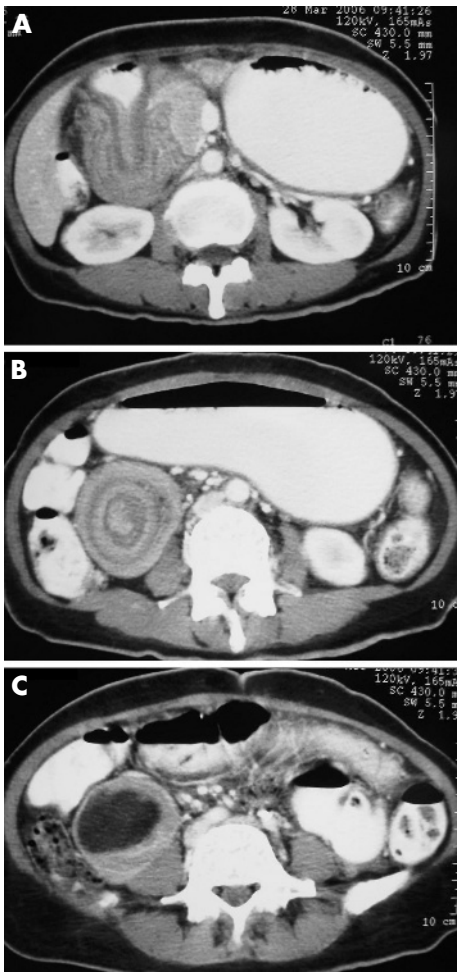

Figure 1-A A—C; CT of the abdomen.