The Risk of Cancer in Children with Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) in children is associated with chronic inflammation, and such inflammation increases the risk of cancer development. Since IBD incidence is increasing in children, the authors of this study performed a meta-analysis regarding the potential cancer risk in children with IBD using PRISMA guidelines. Potential articles and abstracts evaluating the risk of cancer in pediatric patients with IBD (defined as occurring under 25 years of age) were obtained from PubMed, Google Scholar, Scopus, Cochrane Central Register of Controlled Trials as well as from major cancer and gastroenterology meetings. IBD terms such as "Crohn's disease", "ulcerative colitis", and "inflammatory bowel disease" combined with various potential cancer terms including "childhood", "cancer", "malignancy", as well as several types of malignancy were searched via these databases. Each potential data source was reviewed by 2 authors, and the Jadad score and the Cochrane Risk of Bias Assessment Instrument were used to determine randomized controlled trial quality. The Newcastle-Ottawa Scale was used to assess observational study quality. GRADE criteria (Grading of Recommendations, Assessment, Development and Evaluation) were used to determine risk of bias. The primary outcome was to determine the risk of cancer noted in studies using standardized incidence ratios. Secondary outcomes included the pooled incidence rates of all cancers as well as site-specific cancers. Meta-regression analysis was performed to determine if medication type influenced cancer development.

A large number of potential studies (total of 969,127) was initially identified; however, only 66 studies including 38,092 patients were included in the final analysis. A total of 44 studies evaluated patients with Crohn's disease; 31 studies evaluated patients with ulcerative colitis; and 5 studies evaluated patients with IBD (no distinction given). Patients less than 18 years of age were included in 50 studies (75.76%) while the remainder of the studies included patients 18 to 24 years of age. A total of 14 of the 62 observational studies had a Newcastle-Ottawa score of 6 or higher. All randomized controlled trials had a Jadad score of 2 or 3. No inter-rater disagreement for data scoring was noted between the study authors.

A total of six retrospective observational studies including 17,450 patients evaluated the standardized incidence ratio of cancer occurrence. At least 125 patients developed a malignancy although the final number of patients with a malignancy was not clear. Four of these studies evaluated patients with Crohn's disease and noted a 2.4-fold increased risk of cancer (pooled SIR 2.42, $P < .0001$, 95% CI 1.90-3.06; meta-analysis heterogeneity score ($I2 = 0\%$) while five of these studies evaluated patients with ulcerative colitis and noted a 2.1-fold increased risk of cancers (pooled SIR 2.10, $P < .0001$, 95% CI 1.51-2.90; $I2 = 41.54\%$). A pooled standardized risk ratio for all pediatric patients with IBD was 2.39 ($P < .0001$, 95% CI 2.00-2.86; $I2 = 0\%$). The pooled incidence of overall pediatric cancers came from 9 prospective and 44 retrospective studies. The pooled incidence rate of overall cancers in patients with Crohn's disease was 0.014 (95% CI 0.0087-0.021; $I2 = 78.90\%$) while the pooled incidence rate of overall cancers in patients with ulcerative colitis was 0.031(95% CI 0.018-0.052; $I2 = 91.59\%$) and the pooled incidence rate of overall cancers in all of the included studies was 0.018 (95% CI 0.013-0.025; $I2 = 89.10\%$). A meta-regression analysis determined that follow-up study duration positively correlated with cancer development risk, and this finding was statistically significant. No such association was seen with various medications used to treat pediatric IBD including use of steroids, immunomodulators, and anti-tumor necrosis factor medications.

Regarding specific cancer development, not enough data was available to perform a meta-analysis for the development of colorectal cancer. However, the pooled incidence rate of colorectal cancer in CD was 0.0075 (95% CI 0.0049-0.011; $I2 = 41.30\%$) while the pooled incidence rate of colorectal cancer in ulcerative colitis was 0.020 (95% CI 0.012-0.034; $I2 = 87.95\%$) and the pooled incidence rate in all pediatric IBD patients was 0.010 (95% CI 0.0074-0.014; $I2 = 81.30\%$). There appeared to be a statistically significant and positive correlation between male patients and the risk of

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colorectal cancer while a statistically significant and negative correlation was seen between age of IBD diagnosis / onset and risk of colorectal cancer with younger patients at time of diagnosis having an increased risk of colorectal cancer long term. Only one study provided standardized incidence ratio data on hematologic cancers in the setting of IBD. However, enough studies were present to determine the pooled incidence rate of pediatric patients with Crohn's disease and ulcerative colitis. Patients with Crohn's disease had a pooled incidence rate of 0.0061 (95% CI 0.0040-0.0090; I2 = 27.14%) while patients with ulcerative colitis having a pooled incidence rate of 0.0045 (95% CI 0.0040-0.0090; I2 = 31.66%). The pooled incidence rate of all pediatric patients with IBD was 0.0054 (95% CI 0.0039-0.0075; I2 = 35.25%). Meta-regression analysis showed no risk of hematologic cancers in patients having received steroids, immunomodulators, or anti-tumor necrosis factor medications. Finally, cumulative meta-analyses showed that all cancer types had a decreasing incidence over time.

This study shows that pediatric patients with IBD do have an inherent cancer risk, but it is reassuring that the risk of cancer is not associated with standard IBD therapy. It also is helpful to know that the incidence of cancer in this study decreased over time suggesting pediatric patients with IBD may be maintaining good disease control over time. However, the range of heterogeneity of meta-analyses in this study suggests that better data is needed to answer this question more clearly.

Komaki Y, Komaki F, Yamada A, Micic D, Ido A, Sakuraba A. Risk of cancers in patients with pediatric inflammatory bowel diseases: a systemic review and meta-analysis. Journal of Pediatrics 2021; 229: 102-117.

Radiation Exposure during Pediatric ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) is increasing as a pediatric gastrointestinal diagnostic and therapeutic modality. However, ERCP is associated with ionizing radiation exposure, and in adult gastroenterology literature, radiation exposure is reduced if procedures are performed by high-volume endoscopists. It is unknown if this same finding occurs with pediatric gastroenterologists who perform ERCP.

The authors of this study performed a retrospective review of all pediatric ERCPs completed at a single, large children's hospital over a 15-year period (2002-2017). ERCPs in this setting were performed by both adult and pediatric gastroenterologists, and a "high-volume gastroenterologist" was defined as one who performed greater than 100 adult and pediatric ERCPs per year while a "low-volume gastroenterologist" was defined as one who performed less than 100 such procedures. Each gastroenterologist had ERCP data reviewed

including obtaining information about each pediatric patient (age, sex, diagnosis, and ERCP intervention). Fluoroscopy time during ERCP was compared between high-volume and low-volume gastroenterologists.

A total of 385 ERCPs were performed on 321 patients by 8 gastroenterologists (5 adult; 3 pediatric). Three adult gastroenterologists and one pediatric gastroenterologist were high-volume providers while the rest were low volume. A separation into high- versus low-volume providers demonstrated that 175 ERCPs were performed by low-volume gastroenterologists and 210 were performed by high-volume gastroenterologists. The average patient age was 13.4 years with 51% of patients being Caucasian. All patient variables did not differ significantly between low-volume and high-volume gastroenterologists. Throughout the study, the proportion of therapeutic ERCPs increased significantly over time. Median fluoroscopy time per procedure was 4.85 (± 2.68) minutes. High-volume gastroenterologists had a median fluoroscopy time of 2.04 minutes which was significantly lower than low-volume gastroenterologists who had a median fluoroscopy time of 5.21 minutes. Univariate and multi-variate analyses also demonstrated significantly increased fluoroscopy time for patients who needed an ERCP for a pancreas disorder, for patients with any type of ductal stricture, and for any patient less than 4 years of age or greater than 16 years of age. Significantly decreased fluoroscopy time was associated with patients who had undergone prior ERCP. The ASGE Procedure Complexity Scale for patient procedures did not predict fluoroscopy time although the Stanford Fluoroscopy Complexity Scale did show a significant correlation between total fluoroscopy time and increasingly complex pediatric procedures. Finally, ERCPs with fluoroscopy controlled by a radiology technician or radiologist had significantly higher fluoroscopy time compared to endoscopist-controlled fluoroscopy, and C-arm use was associated with significantly more fluoroscopy time compared to use of a fixed fluoroscopy unit.

This study demonstrates that high-volume endoscopists who perform ERCP utilize less fluoroscopy time comparted to low-volume endoscopists. Also, the person controlling the fluoroscopy and type of machine providing imaging appears to effect exposure time. Multi-center as well as prospective studies are needed to confirm these important findings.

Barakat M, Gugig R, Imperial J, Berquist W. Flouroscopy time during endoscopic retrograde cholangiopancreatography performed for children and adolescents is significantly higher with low-volume endoscopists. Journal of Pediatric Gastroenterologists and Nutrition 2021; 72: 244-249.

Answers to this month's crossword puzzle:

1 S	T	2 E	L	3 L	4 A	5 T	E	■	6 G	7 L	I	8 A	L	■
C	■	N	■	9 A	R	M	■	10 F	■	E	■	D	■	11 T
12 L	A	C	T	I	C	■	13 A	L	K	A	L	I	N	E
E	■	A	■	D	■	14 R	■	A	■	K	■	P	■	N
15 R	I	S	K	■	16 B	I	O	P	17 S	Y	■	18 O	P	T
O	■	E	■	19 A	■	B	■	■	A	■	■	S	■	■
20 S	O	■	21 A	U	T	O	I	22 M	M	U	N	E	■	23 S
I	■	■	■	T	■	S	■	24 B	P	■	■	■	25 M	Y
26 N	E	27 C	R	O	S	E	■	28 A	L	B	U	29 M	I	N
G	■	O	■	P	■	■	■	■	I	■	■	30 A	N	T
■	31 A	L	P	H	A	■	32 T	E	N	S	O	R	■	H
33 A	■	O	■	A	■	34 G	■	■	G	■	■	K	■	E
35 X	E	N	O	G	R	A	F	36 T	■	37 T	R	E	G	S
I	■	I	■	Y	■	L	■	L	■	I	■	R	■	I
38 S	A	C	S	■	39 G	L	Y	C	O	L	Y	S	I	S