Cancer in Children with Inflammatory Bowel Disease: Are We Making a Difference?

Inflammatory bowel disease (IBD) in childhood is increasingly common worldwide,[1] with incidence growing fastest among children diagnosed before their fifth birthday.[2] Understanding the long-term implications of this life-long inflammatory disease and its treatments are of vital importance. One potential long-term implication is the increased risk of malignancies. The link between IBD (particularly adult-onset IBD) and colorectal cancer is well-established and thought to be secondary to chronic undertreated inflammation of the colon. Immunosuppressant and biologic therapies have also been associated with malignancies, specifically lymphoma and non-melanoma skin cancer. However, less is known about these risks when IBD is diagnosed in childhood. Current therapeutic options for pediatric IBD include specialized care providers, a growing armamentarium of biologic treatments, therapeutic drug monitoring, increasing access to endoscopy and noninvasive monitoring for disease activity, and treat-to-target strategies in which the goal is mucosal healing and elimination of inflammation instead of symptomatic improvement alone. The effects of these changes to the care of children with IBD on the risk of cancer has not been fully explored.

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In this volume of *The Journal*, Komaki et al[3] synthesize data from 66 studies describing the incidence of cancer (any malignancy, colorectal cancer, and hematologic malignancies) in pediatric-onset IBD. They report a significantly greater incidence of cancer in patients with pediatric-onset IBD relative to the general population (Crohn's disease: standardized incidence ratio 2.42, 95% CI 1.90-3.06; ulcerative colitis: standardized incidence ratio 2.10, 95% CI 1.51-2.90).[3] The pooled incidence rate for any malignancy was 0.014 (95% CI 0.0087-0.021) among those diagnosed with Crohn's disease and 0.031 (95% CI 0.018-0.052) among those diagnosed with ulcerative colitis. Where the data were available, the authors reported decreasing trends over time in the incidence of cancer, including colorectal and hematologic malignancies. This implies improved outcomes in the era of modern therapies. However, time trends analyses were not standardized to the incidence of cancer in the general population and may have been confounded by the length of study—malignancy will become more common with longer follow-up.

The authors should be commended for their extensive and rigorous review of the literature. However, readers should interpret these results with caution. Incidence rates should always be reported as the number of events per person-time. This is particularly important when analyzing an outcome like cancer that becomes more frequent with longer follow-up. In fact, the authors demonstrated that incidence rates for overall malignancy were greater among studies with a longer duration of follow-up and that study duration partly accounted for the high heterogeneity between studies. A second challenge stems from the lack of population-based data available for analysis. Only by including all individuals or a representative sample with childhood-onset IBD, and all malignancies among these patients, can we be certain that incidence estimates are accurate. The authors pooled incidence rates from the following types of studies with potentially systematically different populations: (1) randomized controlled trials; (2) observational studies and case series conducted using samples of patients treated at tertiary-care centers; and (3) observational studies conducted using population-based samples. The sparsity of population-based data reinforces the need for more rigorous long-term outcome studies of children with IBD.

The authors conducted meta-regression to determine whether medications were associated with risk of cancer and found no association between use of steroids, immunomodulators, or anti-tumor necrosis factor alpha biologics and cancer. Although this is reassuring, the lack of association observed between thiopurines (either alone or in combination with anti-tumor necrosis factor alpha) and lymphoma is not consistent with large, observational studies published in pediatric[4] and adult IBD[5,6] or previous meta-analyses in patients with IBD of all ages.[7] This suggests a methodologic flaw in either the literature included in the meta-analysis or the meta-analysis itself. For example, the authors were not able to determine the association between duration of thiopurine therapy and cancer due to a lack of information among studies included in the systematic review and meta-analysis. In addition, it is unclear if these meta-regression analyses are based on study-level ecological data (ie, comparing the proportion of patients in a given study receiving these treatments and the overall risk of cancer in a given study) or based on reported associations between treatment and cancer. Despite the lack of association seen in this review, IBD care providers should approach thiopurines with caution, especially in male patients, who are at greater risk of treatment-associated lymphoma.

The long-term outcomes of an IBD diagnosis during childhood, including the future risk of cancer, are a source of concern for parents and providers. Komaki et al provide important data on this risk.[3] However, physicians should

IBD Inflammatory bowel disease

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be cognizant of the methodologic weaknesses of this meta-analysis, and researchers should use these weaknesses as lessons to help them design better observational long-term research studies. Only well-designed studies with representative samples will allow us to provide families with evidence-based estimates of cancer in their child. ■

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Prolonged Ductal Patency in Preterm Infants: Does It Matter?

In this volume of *The Journal*, Clyman et al present analysis of data collected in the Patent Ductus Arteriosus: TO LEave it alone or Respond And Treat Early (PDA-TOLERATE) trial, examining the hypothesis that the risk of bronchopulmonary dysplasia (BPD) in infants born before 28 weeks of gestation is linked to interaction between prolonged positive-pressure ventilation and prolonged exposure to a moderate-to-large patent ductus arteriosus (PDA).[1] This study represents the capstone of a triad of recent inquiries into these relationships by Clyman et al.[1-3] Such post hoc analyses are fraught with potential for false discoveries, but these reports are notable not for what they find but for what they do not and, therefore, deserve close attention.

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The prior 2 reports draw upon data collected prospectively for over 15 years at a single center (University of California San Francisco). The first shows that the risk of death or BPD was greater among infants in whom a moderate-to-large PDA was present for 7 days or more (OR 2.57 vs infants exposed for <7 days; 95% CI 1.71-3.87, $P < .0001$).[2] The rates of the combined outcome (or, conversely, survival without BPD) did not differ among groups with durations of PDA exposure ≥7 days ($P = .66$; **Figure**; available at www.jpeds.com). In the second report, grade 2-3 BPD (defined as requiring nasal cannula flow rates >2 L/minute, noninvasive positive airway pressure, or invasive mechanical ventilation at a postmenstrual age of 36-$^{0}/_{7}$- 36-$^{6}/_{7}$ weeks[4]) was also more likely in infants exposed to moderate-to-large PDA for ≥7 days (OR 5.10; 95% CI 2.58-10.1, $P < .0001$); again, longer exposures (beyond 7 days) were not associated with incremental risk ($P = .67$ by 2-by-3 χ^2).[3] This relationship held only for infants who required invasive ventilation for ≥10 days; among those intubated for <10 days, the risk of grade 2-3 BPD was low and did not significantly increase whether exposed to PDA for <1 week (2%) or for several weeks (6%; $P = .13$).[3] Examination of these relationships in the PDA-TOLERATE cohort confirmed that prolonged exposure to PDA (≥10 days) was associated with increased risk of either any BPD or grade 2-3 BPD only in

BPD	Bronchopulmonary dysplasia
PDA	Patent ductus arteriosus
PDA-TOLERATE	Patent Ductus Arteriosus: TO LEave it alone or Respond And Treat Early

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