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EDITORIALS

Increased risk of cancer in children with inflammatory bowel disease

The increase persists well into adulthood

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People with inflammatory bowel disease worry about developing cancer.[1] These concerns stem in part from drug labels warning of the rare but real increased risk, as well as from websites and peer reviewed papers that make their way into the headlines. Families of children with inflammatory bowel disease are particularly fearful after discovering that biological agents and immunomodulators are associated with hepatosplenic T cell lymphoma, particularly among children and young adults.[2] Previous studies have identified higher rates of cancer among patients with inflammatory bowel disease than in the general population, but these studies have lacked the population size or follow-up to assess trends in lifetime risks.

The linked research paper (doi:10.1136/bmj.j3951), a Swedish nationwide cohort study of children diagnosed with inflammatory bowel disease between 1964 and 2014, reports that children with inflammatory bowel disease have an increased risk of cancer in both childhood and adulthood.[3] Through adulthood (median age at end of follow-up was 27 years), 497 people with childhood onset inflammatory bowel disease had first cancers (3.3 per 1000 person years), compared with 2256 in the general population (1.5 per 1000 person years; hazard ratio 2.2, 95% confidence interval 2.0 to 2.5). Hepatic, gastrointestinal, lymphatic, and skin cancers had the highest relative rates. The authors noted that risk of cancer did not change with calendar year of diagnosis of inflammatory bowel disease.

Relative rates of cancer diagnosed before the 18th birthday were higher for gastrointestinal and haematological cancers but not other cancers. The relative rate of female genital cancer at any age did not differ from controls despite previous evidence that women with inflammatory bowel disease have higher rates of cervical dysplasia than those without.[4]

The authors found that overall cancer risks associated with inflammatory bowel disease have not declined over time, and in particular don't seem to have fallen following the introduction of immunomodulatory and biological agents. The supplementary analyses indicate that risk of some cancers is higher among children who received diagnoses after 2002, including gastrointestinal and melanoma skin cancers, but not haematological cancers. Greater use of biological agents and immunomodulators might be expected to increase risk of haematological cancers, whereas their effects on inflammation should decrease the risk of gastrointestinal cancer.

We are unable to determine the relation between cancer risk and use of immunomodulators, biological agents, or their combination owing to incomplete information on exposure to infliximab, as well as insufficient follow-up and power. The study would require at least five times as many participants (or person years of follow-up) to be powerful enough to detect a doubling of lifetime risk of cancer associated with immunomodulators or biological agents.

The sample size required to detect any association between childhood onset cancers and drugs would have to be even larger. Children and their families worrying about cancer risks today might have a long time to wait for reliable information about the long term effects of different treatments. Answers will probably require pooling study populations well beyond the geographical bounds of a single country. Until then, these families should perhaps focus on the very low incidence of cancer in childhood. Olén and colleagues found that only 0.2% (20/9045) of children with inflammatory bowel disease were diagnosed as having cancer before their 18th birthday.

The study also confirms the need for international collaboration in the study of cancer surveillance for these children. Evaluating different strategies, such as endoscopy, or exploring the benefits and risks of new, less invasive technologies to test for early indicators of gastrointestinal cancer will require very large sample sizes that can only be achieved by pooling national databases and resources. Identifying the best strategy for subgroups of children taking different drugs will increase sample size requirements further.

Increasing surveillance might lead to earlier diagnosis, enhanced detection, and increased reported rates of cancer, as the authors point out in their discussion. The ultimate goal of surveillance is of course reduced cancer mortality, an outcome that requires very long follow-up. Disentangling who should be offered regular surveillance, when, how often, and for how long will require collaboration among clinical epidemiologists and health services researchers on a scale comparable to the genomics researchers who pooled nearly 100 000 patients with inflammatory bowel disease from all over the world.[5] An international inflammatory bowel disease consortium to validate

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and translate administrative databases and electronic medical records into real world evidence could help fill this and other research gaps.

International efforts to confirm the findings of this Swedish cohort and extend their reach to the increasing number of children diagnosed as having inflammatory bowel disease globally will help to improve decision making for the many patients and their families who must choose between different options for both treatment and surveillance. Olén and colleagues' thoughtful and thorough investigation sets an excellent example of the methods that can be used to pursue international database studies in childhood onset inflammatory bowel disease.

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