7. Dockray GJ. Clinical endocrinology and metabolism. Gastrin. Best Pract Res Clin Endocrinol Metab 2004;18:555–568.
8. Wang TC, Koh TJ, Varro A, et al. Processing and proliferative effects of human progastrin in transgenic mice. J Clin Invest 1996;98:1918–1929.
9. Singh P, Velasco M, Given R, et al. Progastrin expression predisposes mice to colon carcinomas and adenomas in response to a chemical carcinogen. Gastroenterology 2000;119:162–171.
10. Gregory RA, Tracy HJ, Agarwal KL, et al. Amino acid constitution of two gastrins isolated from Zollinger-Ellison tumour tissue. Gut 1969;10:603–608.
11. Gregory RA, Tracy HJ. Isolation of two "big gastrins" from Zollinger-Ellison tumour tissue. Lancet 1972;2:797–799.
12. Zimmer T, Stolzel U, Bader M, et al. Brief report: a duodenal gastrinoma in a patient with diarrhea and normal serum gastrin concentrations. N Engl J Med 1995;333:634–636.
13. Jais P, Mignon M. Normal serum gastrin concentration in gastrinoma. Lancet 1995;346:1421–1422.
14. Berna MJ, Hoffmann KM, Serrano J, et al. Serum gastrin in Zollinger-Ellison syndrome: I. Prospective study of fasting serum gastrin in 309 patients from the National Institutes of Health and comparison with 2229 cases from the literature. Medicine (Baltimore) 2006;85:295–330.
15. Berna MJ, Hoffmann KM, Long SH, et al. Serum gastrin in Zollinger-Ellison syndrome: II. Prospective study of gastrin provocative testing in 293 patients from the National Institutes of Health and comparison with 537 cases from the literature. evaluation of diagnostic criteria, proposal of new criteria, and correlations with clinical and tumoral features. Medicine (Baltimore) 2006;85:331–364.
16. Frucht H, Howard JM, Slaff JI, et al. Secretin and calcium provocative tests in the Zollinger-Ellison syndrome. A prospective study. Ann Intern Med 1989;111:713–722.
17. Goldman JA, Blanton WP, Hay DW, et al. False-positive secretin stimulation test for gastrinoma associated with the use of proton pump inhibitor therapy. Clin Gastroenterol Hepatol 2009;7:600–602.
18. Feldman M, Schiller LR, Walsh JH, et al. Positive intravenous secretin test in patients with achlorhydria-related hypergastrinemia. Gastroenterology 1987;93:59–62.
19. McLean AM, Fairclough PD. Endoscopic ultrasound in the localisation of pancreatic islet cell tumours. Best Pract Res Clin Endocrinol Metab 2005;19:177–193.
20. Behe M, Gotthardt M, Behr TM. Imaging of gastrinomas by nuclear medicine methods. Wien Klin Wochenschr 2007;119:593–596.
21. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001;86:5658–5671.
22. Rehfeld JF, Gingras M–H, Bardram L, et al. The Zollinger–Ellison syndrome and mismeasurement of gastrin. Gastroenterology 2011;140:1444–1453.
23. Rehfeld JF. The art of measuring gastrin in plasma: a dwindling diagnostic discipline? Scand J Clin Lab Invest 2008;68:353–361.
24. Varro A, Ardill JE. Gastrin: an analytical review. Ann Clin Biochem 2003;40:472–480.
25. Jorgensen NR, Rehfeld JF, Bardram L, et al. Processing-independent analysis in the diagnosis of gastrinomas. Scand J Gastroenterol 1998;33:379–385.
26. Yang YX, Metz DC. Safety of proton pump inhibitor exposure. Gastroenterology 2010;139:1115–1127.

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Childhood Cancer Survival: A Risk Factor for GI Disease

See "Survivors of childhood cancer have increased risk of gastrointestinal complications later in life," by Goldsby R, Chen Y, Raber S, et al, on page 1464.

Each year, 12,500 children and adolescents are diagnosed with cancer in the United States.[1] Significant biomedical advances over the past several decades have increased the 5-year survival rate to 80% for these children.[1] The large number of childhood cancer survivors reaching adulthood has made study of late effects essential to understand the breadth of medical and psychological complications these patients may face. The Childhood Cancer Survivor Study (CCSS) is among the first large cohorts of childhood cancer survivors.[2–4] It is a multicenter, retrospective, cohort study with longitudinal follow-up of cancer survivors diagnosed between 1970 and 1986. Recruitment began in 1992 and >14,000 patients completed a baseline questionnaire and gave

consent to obtain medical records. This cohort represents about 70% of the eligible population. Follow-up questionnaires were administered in 2000, 2003, 2005, and 2007. More than 8900 patients completed the questionnaire each year. In addition, data on almost 4000 siblings were collected. The existing database provides a unique resource for researchers interested in the outcome of childhood cancer survivors.

Despite the robustness of the data collected, the database has limitations that must be acknowledged when interpreting studies derived from the data. Because the database relies on self-report questionnaires to elicit information about physical complaints and psychological issues, the impact of bias in reporting outcomes or symptoms is an important concern for investigators using the database for research. Many of the children were quite young when they were diagnosed and treated for cancer, and they may not remember details about the diagnosis or treatment. The same may be true for older children as well, because their parents were still the primary medical decision makers and may not have shared everything with their child. Consequently, survivors may have significant knowledge deficits about basic aspects of their diagnosis and treatment.

To circumvent recall bias for important details of care, the design of the CCSS required abstraction of some details from the medical records of the participants.[2] Because therapeutic exposures are critical to attribution of late outcomes, the exposure to chemotherapeutic agents, radiation, and surgery were obtained from medical records rather than patient recall. For chemotherapeutic agents, the participants were queried about 42 commonly prescribed chemotherapeutic agents. For 22 agents, the quantitative dose was abstracted and cumulative dose was calculated as a measure of exposure for common drugs. For surgery, each procedure requiring general anesthesia, except those for placement of vascular access devices, was abstracted and the date, name of the procedure and International Classification of Disease code entered in the database. For radiation, details about the dose, body region treated, field size, and dates of treatment were entered. Some specific studies on radiation exposure have required additional record review to acquire the details of radiation exposure and these were provided.

Validation of outcomes is a major concern of the CCSS. Because of the large number of participants and multiple potential outcomes, validation through medical record review is prohibitively labor intensive and expensive. The study group decided to validate the outcomes that were considered major endpoints, namely, mortality, subsequent neoplasms, adverse pregnancy outcomes, and adverse cardiopulmonary outcomes. Validation of mortality, subsequent neoplasms, and adverse pregnancy outcomes demonstrated that self-reporting of these outcomes was reliable. Validation of cardiopulmonary outcomes proved problematic because medical record review and telephone interviews failed to confirm a diagnosis of congestive heart failure in many subjects who reported the complication and a significant fraction of patients who reported the outcome had died before the time of validation. Validation of other outcomes has not been performed.

Despite the limitations of self-reported data, the utilization of the data in the CCSS has been robust. Since its inception, >160 studies based on the data from the CCSS have been published. The studies have focused on various topics. One third or more have examined the rate of subsequent neoplasms, reoccurrences of the original tumor, or occurrence of a new cancer. Many others have focused on issues affecting psychological and health-related quality of life. Even with widespread use of the database, the report by Goldsby et al[5] in this issue of GASTROENTEROLOGY is the first to focus on gastrointestinal (GI) complications in survivors of childhood cancer.

The investigation of late GI complications in this patient population is particularly pertinent given the acute effects of cancer therapy on the GI tract. Radiation of the abdomen can cause mucosal inflammation and dysmotility. Surgery can result in anastomotic strictures or bowel obstruction from adhesions. Chemotherapy has a broad range of acute GI toxicities. Nausea and vomiting are common. Mucositis and GI infections can be recurrent and cause cumulative damage to the intestinal mucosa including the esophagus. Liver dysfunction occurs as a direct toxicity of chemotherapeutic agents or of infection. Varied pathophysiology is found including cholestasis, hepatocellular necrosis, steatosis, and veno-occlusion.[6,7] Severe pancreatitis is a common complication of some widely used agents.

In their study, Goldsby et al[5] analyzed data from the initial questionnaire for the types and incidence of GI complaints. The survey included questions about upper GI complications, liver conditions and lower GI complications. Of the 14,358 childhood cancer survivors and 3899 sibling controls who completed the survey, GI complications were reported by 5824 survivors. The majority of patients reported the onset of GI symptoms >5 years after diagnosis. About 40% reported ≥2 GI complications. The overall relative risk of a survivor reporting a complication was 1.7 for a single complication and 1.6 for reporting ≥2 complications. Interestingly, the relative risk of reporting ≥2 liver problems was 12.2.

The relative risk for upper or lower GI disease ranged from 0.9 to 5.6 compared with siblings. The greatest risk was for colostomy or ileostomy surgery. Unfortunately, the data set does not provide a clear explanation for the higher incidence of this outcome. Overall multivariable

Poisson regression analysis indicates that older age at diagnosis, high doses of alkylating agents, and abdominal radiation were associated with greater risk of having any lower GI complication. The risk for ostomy surgery was not analyzed separately. The obvious speculation is that survivors would be at higher risk for obstruction from adhesions or strictures. The data argue against that conclusion because the survivors did not have a greater relative risk of surgery for adhesions and strictures compared with siblings. Even though survivors are likely to reliably report the presence of an ostomy, they may not know or remember the indication for surgery.

The other lower GI complication that stands out is the increased risk for diarrhea. Because of the repeated insult to the intestinal mucosa, the increased presence of diarrhea in this population is plausible. Still, there are difficulties in interpreting this complaint. The original questionnaire simply asks for a "yes" or "no" answer to the question "Do you have chronic diarrhea?" No definition of chronic diarrhea is given. It is left to the individual to determine whether their bowel pattern qualifies as chronic diarrhea. Additionally, the nature and associated symptoms of the diarrhea are not known. That information is critical to understanding why survivors may have more complaints of diarrhea. Damage to the intestinal tract during treatment may lead to scaring or fibrosis of intestinal tissue. There is also the intriguing possibility that treatment-related gut injury may alter neural pathways in the brain–gut access or result in imprinting of sensory regions of the brain, making survivors more susceptible to irritable bowel syndrome.

The questions asked about upper GI disease make it difficult to interpret other than that survivors are more at risk for upper GI complaints than the controls. The questions about esophageal disease, indigestion or heartburn, and other upper GI troubles have potential for overlap and may represent an increased risk for gastroesophageal reflux disease and little else. Information about esophageal strictures or other esophageal or gastric disease is not available. The same can be said about nausea and vomiting, although they may occur in the absence of esophageal or gastric disease. Interestingly, the relative risk for nausea and vomiting was higher than other categories, suggesting that they may occur in the absence of identifiable pathology. As with the lower GI complaints, the mechanism for the increased risk of upper GI complaints is not clear. An interesting possibility is one that cannot be addressed in this cohort. They were all diagnosed and treated before the availability of effective anti-emetics like ondansetron. In the era when these patients were treated nausea and vomiting were a prominent side effect of treatment and treatments had limited effectiveness. By contrast, patients treated in the era of ondansetron are likely to tolerate treatment with little to no nausea or vomiting. It will be of great interest to know whether survivors from more recent eras report an increased incidence of upper GI problems.

The greatest relative risks for survivors compared with controls were for liver cirrhosis and liver biopsy. Older age, total body irradiation (mostly patients undergoing bone marrow transplant), alkylating agents, anthracycline, and abdominal surgery were all independent risk factors for liver and gallbladder disease. Missing from the database is information about viral hepatitis in this population, in particular hepatitis C. The cohort dates to a time when hepatitis C was acquired from blood transfusions much more frequently than currently happens. Other infectious complications during treatment may well increase the incidence of liver disease in this cohort compared with patients treated more recently.

The high incidence of liver biopsy in this population seems surprising at first, but a closer examination of the data suggests a possible explanation. The survivors reported 170 liver biopsies. The data in the paper do not make it possible to know if the number represents single individuals or if some fraction reported >1 biopsy. Still, the number is close to the number who had total body irradiation, namely 184, and presumably had a bone marrow transplant. Bone marrow transplantation is not a reported treatment in the manuscript, although the information was collected in the questionnaire. Liver dysfunction is an important late complication of bone marrow transplantation. Chronic graft-versus-host disease (GVHD) is a major etiology for liver disease because up to 80% of patients with GVHD have liver involvement. In addition, veno-occlusive disease and infectious hepatitis contribute to the burden of chronic liver disease in these patients. One can speculate that most of the liver biopsies occurred in patients with a history of bone marrow transplantation. The follow-up of this observation with additional detail will be enlightening and add important information for physicians following these patients.

Finally, although the CCSS data clearly provide a powerful source of information about late effects for survivors of pediatric cancer from the perspective of a large, diverse database, we offer 1 additional lens through which to view these data (Table 1). Certainly, the incidence and risk of late GI toxicities in childhood cancer survivors is increased compared with siblings; however, as noted in Table 1, the actual risk of any survivor experiencing these problems remains modest. The CCSS sibling data clearly show that the incidence of this group of GI toxicities is very low, and that the statistically significant relative risk still translates to a low incidence for the group of survivors. It is important to avoid a potential framing bias when discussing possible side effects with newly diagnosed patients and their families, and to use

Table 1. Percentage of Childhood Cancer Survivors and Siblings Who Reported GI Outcomes

Condition	Survivors (%) (N = 14,358)	Siblings (%) (N = 3899)	Overall survivors (%) (N = 14,358)	Overall siblings (%) (N = 3899)
Upper GI complications			5.28	4.14
Ulcer	4.3	3.6		
Esophageal disease	2.0	1.2		
Indigestion/heartburn	14.5	12.7		
Nausea/vomiting	1.3	0.5		
Other upper GI trouble	4.3	2.7		
Liver complications			1.82	1.33
Gallstones and other gall bladder issues	2.3	2.2		
Liver cirrhosis	0.2	0.06		
Jaundice	3.1	4.0		
Liver biopsy	1.0	0.07		
Other liver trouble	2.5	0.3		
Lower GI complications			2.3	1.61
Intestinal polyps/diverticular disease	0.7	0.5		
Colitis	0.8	1.3		
Constipation	6.4	4.6		
Diarrhea	4.6	2.3		
Rectal/anal fistula/stricture/other obstruction surgery	1.1	1.0		
Colostomy/ileostomy	0.8	0.1		
Other lower intestinal trouble	1.7	1.5		

discretion when these patients are seen for long-term follow-up care.[8] Risk is elevated; incidence remains low.

The article by Goldsby et al[5] in this issue of GASTROENTEROLOGY is an important first step in defining the types of GI complications present in childhood cancer survivors. A better understanding of these outcomes is more than academic interest. The knowledge will improve care of a large patient population. In the United States, about 1 in 640 adults aged 20–29 years are childhood cancer survivors. Gastroenterologists are likely to see these patients in their practice. Finally, more detailed knowledge about the pathophysiology of the GI diseases in childhood cancer survivors has the potential to advance understanding about the effect of prior experience on brain–gut interactions and the biology of the gut response to injury.

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References

1. Altekruse S, Kosary C, Krapcho M, et al. SEER cancer statistics review, 1975–2007. Bethesda, MD: National Cancer Institute, 2010.
2. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:2319–2327.
3. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. J Clin Oncol 2009;27:2308–2318.
4. Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 2002;38:229–239.
5. Goldsby R, Chen Y, Raber S, et al. Survivors of childhood cancer have increased risk of gastrointestinal complications later in life. Gastroenterology 2011;140:1464–1471.
6. Di Fiore F, Van Cutsem E. Acute and long-term gastrointestinal consequences of chemotherapy. Best Pract Res Clin Gastroenterol 2009;23:113–124.
7. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58:71–96.
8. Fryer C. Late effects in childhood cancer survivors: a review with a framing effect bias? Pediatr Blood Cancer 2011 Jan 19. Epub ahead of print.

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