

# Reduced Incidence of Rectal Cancer, Compared to Gastric and Colonic Cancer, in a Population of 73,076 Men and Women Chronically Immunosuppressed<sup>1</sup>

Thomas Stewart,<sup>2</sup> Robin Henderson,  
Helen Grayson, and Gerhard Opelz

Ottawa General Hospital, Ottawa, Ontario, K1H 8L6 Canada [T. S.]; Medical Statistics Unit, Department of Mathematics and Statistics, Lancaster University, Lancaster LA1 4YF, United Kingdom [R. H.]; Department of Mathematics and Statistics, University of Newcastle-upon-Tyne, Newcastle-upon Tyne NE1 7RU, United Kingdom [H. G.]; and Department of Transplantation Immunology, University of Heidelberg, Heidelberg 305-6900, Germany [G. O.]

## ABSTRACT

The incidence of gastric, colonic, and rectal cancers was determined in a cohort of 73,076 men and women chronically immunosuppressed after heart or renal transplantation, to test the hypothesis that there would be a reduced incidence of gastric cancer by dampening chronic gastritis secondary to infection caused by *Helicobacter pylori*. Follow-up was from 1–13 years. No change in the incidence of gastric cancer was found (32 cases observed, 32.86 expected). An increase in colon cancer was found (75 cases observed, 62.27 expected). A significant reduction in the incidence of rectal cancer was found (15 cases observed, 41.5 expected). This led to a  $\chi^2$  of 16.92 with 1 degree of freedom, significant at the 0.1% level. The effect was greater in men than women and more marked in heart recipients than in those receiving renal transplants. This unexpected finding led to a review of experiments in mice and rats that present evidence for immune promotion of large-bowel cancers induced by carcinogens by gut-associated lymphoid tissue. We conclude that an analysis of immune function in gut-associated lymphoid tissue in the stomach, colon, and rectum in healthy and immunosuppressed patients may lead to a better understanding of immunosurveillance in the colon and immune promotion of rectal cancers.

## INTRODUCTION

We have previously reported that there is a significant reduction in the incidence of *de novo* breast cancer in women chronically immunosuppressed after organ transplantation (1).

This finding suggested that there is immune promotion of oncogenesis in a substantial cohort of women as in retrovirus-associated breast tumors in mice. All other major cancers in women were found to be increased, in some cases substantially, with a marginal increase in others. Of the latter, those arising in the GI<sup>3</sup> tube showed a slight overall increase of 5%. Patients followed for a long time after renal grafts in ANZ (2) and the Nordic countries (3) have shown an increased incidence of colon cancer. In our series, one could predict that there would have to be a lessening of the incidence of another GI tube cancer to yield the small increment we reported. A promising candidate was gastric cancer, which is now believed to evolve after infection with *Helicobacter pylori* (4, 5). Such infection induces gastritis, hyperplasia of the gastric mucosa, peptic ulcer, mucosal metaplasia, and cancer (6). If chronic immunosuppression would sufficiently dampen the chronic gastritis to break this chain of events, then a reduced incidence of gastric cancer might be found in a large population of men and women who are chronically immunosuppressed after organ transplantation in contrast to an increase of colon and rectal cancer. To investigate this hypothesis, the incidence of these three cancers was assessed in just such a population of men and women.

## PATIENTS AND METHODS

Results are based on data provided to the Collaborative Transplant Study in Heidelberg since 1983. This is a multicenter project including more than 300 transplant centers worldwide. The present study concentrated on transplants performed in Europe or North America until November 1993, with follow-up until November 1994 (*i.e.*, at least 1 year of follow-up, with observation in some patients beyond 10 years, derived from data obtained from some centers antedating 1983). This gave a cohort of 62,088 first cadaver kidney recipients of whom 21,104 were in North America and 40,984 were in Europe and 10,988 first heart recipients of whom 7,304 were in North America and 3,684 were in Europe. Information on posttransplant malignancies was provided by participating centers. To reduce the risk of underreporting, only those centers that confirmed in writing that their data were accurate and complete were included in the analysis. Incidence of a cancer occurring up to 3 months after any graft failure was recorded. All patients were immunosuppressed. Table 1 shows the frequencies of major drugs used.

Background incidence rates were obtained from Parkin *et al.* (7) – the most accurate international source of cancer incidence rates – covering the years 1983–1987, the period of the

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<sup>2</sup> To whom requests for reprints should be addressed, at Room LM18, Ottawa General Hospital, 501 Smyth Road, Ottawa, Ontario, K1H 8L6 Canada. E-mail: Tstewotkcan@msm.com.

<sup>3</sup> The abbreviations used are: GI, gastrointestinal; GALT, gut-associated lymphoid tissue; ANZ, Australia-New Zealand; RR, relative risk; CI, 95% confidence interval.

Table 1 Immunosuppressive drugs

Drug	No. of	
	Kidney recipients	Heart recipients
Cyclosporine	50,439	10,245
Azathioprine	38,978	9,647
Steroids	55,362	10,028
ATG/ALG (prophylactic)	16,597	5,849
OKT3 (prophylactic)	2,494	1,588

first part of the current study. More recent figures of similar accuracy are not available. Background rates were used to calculate expected incidence, with appropriate weighting by population size, by examination of the cumulative number of person-years of follow-up in 5-year age bands, with due allowance for advancement of age with posttransplant year (for instance, if someone is 40 years old at transplantation, that person's contribution to expected incidence 10 years later will be as a 50-year-old person). Observed incidence was compared with background by using the  $\chi^2$  test. There is no claim that transplant recipients form representative random samples from the background population, so observed:expected comparison would be meaningless for a single malignancy. However, investigation of the relative incidence of different cancers allows valid inference.

## RESULTS

There was no change in the observed incidence of gastric cancer in transplant recipients when compared to that in the background population (Table 2; 32 observed, 32.86 expected; RR = 0.97; CI, 0.64–1.31). Colon cancer was increased, although not statistically significantly (75 observed, 62.27 expected; RR = 1.20; CI, 0.93–1.48). Rectal cancer was significantly reduced, however (15 observed, 41.5 expected; RR = 0.36; CI, 0.18–0.54). A  $\chi^2$  test of equality gave test statistic 16.92 with 1 degree of freedom ( $P = 0.00004$ ). Because a total of 13 cancer groups were considered in this and the previous study, there is an increased probability of one or more spuriously significant differences. Appropriate adjustment of the  $\chi^2$  test to allow for multiple comparisons gave  $P = 0.0005$ , discounting this possibility.

Incidence remained consistently lower than background over all posttransplant years (Table 3).  $\chi^2$  for equality gave 19.846 with 5 degrees of freedom ( $P = 0.001$ ). Incidence was lower in heart recipients (2 observed, 8.55 expected; RR = 0.23) than in kidney recipients (13 observed, 32.95 expected; RR = 0.39). There is a gender difference in incidence, which is lower in males (9 observed, 30.82 expected; RR = 0.29) than females (6 observed, 10.68 expected; RR = 0.56).

There was also a lower incidence in patients who received cyclosporine, azathioprine, and steroids (6 observed, 22.31 expected) compared to patients receiving a subset of these drugs (9 observed, 19.19 expected). These differences, however, are not significant due to the small number of cancers observed (Table 4).

Of a total of 62,088 kidney recipients, 15,989 (25.8% of the total) had graft failure without death and resumed chronic dialysis with immunosuppressive treatment discontinued.

## DISCUSSION

It is quite clear that chronic immunosuppression has no effect on the incidence of gastric cancer. The chain of events leading to gastric cancer is not interrupted. Teenan *et al.* (8) examined 33 renal transplant patients by upper GI endoscopy 2–4 months after transplantation. Random biopsies were obtained from the gastric antrum and the first part of the duodenum. Duodenitis was identified in 16 patients, gastritis was identified in 10 patients, and *Helicobacter* was identified in the gastric antrum of 16 patients (48%) and was strongly associated with gastritis. Thus, during the period of time posttransplantation during which immunosuppressive drugs are used intensively, gastritis persisted.

The observed increase in colon cancer was anticipated. The highly significant reduction in the incidence of rectal cancer was completely unexpected and contradicts the reported increase of rectal cancer in the published ANZ and Nordic countries data. We believe this may be explained by substantial differences in the patient populations. In the ANZ data, the follow-up is as long as 28 years, and all patients that received a renal graft were entered into the ANZ Combined Dialysis and Transplant Registry. We know that approximately 25% of such patients resume dialysis, and immunosuppressive drugs are discontinued. Furthermore, the ANZ data report rectum and anal cancer together. The etiology of anal cancer may be attributed to infection with human papillomavirus 16 (9), suggesting that the etiology of anal cancer differs from that of cancer of the rectum. The Nordic countries likewise linked all renal transplants with national cancer registries, again including all patients that resumed dialysis, with follow-up to 22 years. The greatest incidence of digestive tract tumors in men was observed at  $\geq 15$  years of follow-up. Without knowing the data on the incidence of rectal cancer in men and women having a functional kidney graft and continuous immunosuppression or the incidence up to 13 years of follow-up, valid comparisons between our data and the ANZ and Nordic countries data are not possible.

How can we explain the decrease in rectal cancer that we have found? First, errors in reporting rectal and colon cancers are conceivable. Thus, if some rectal cancers are described as colon cancers, this would reduce the incidence of reported rectal cancers and increase the incidence of colon cancers. We believe it to be very unlikely that such an error could be made consistently in all centers reporting, from Western Europe and North America, based on data provided by surgeons and pathologists. It would not explain the difference in rectal cancer incidence in heart recipients (23% background rate) as against kidney recipients (39%), whereas the more intense immunosuppression used in heart transplants would suggest a dose-response effect. Errors in reporting would not explain the clear differences seen between men and women in the reduction of rectal cancer (incidence, 29% background for men and 56% background for women), whereas differences in the hormone environment, lifestyle, or unknown factors could be important.

A more likely explanation for the observed reduction is that there is immunopromotion of oncogenesis in rectal cancer. We are unaware of the existence of an animal model of colon or rectal cancer that is caused by a virus, unlike the mouse mammary tumor virus model of breast cancer (10) or the radiation

Table 2 Incidence of gastric, colon, and rectal cancers in 73,076 male and female transplant recipients

ICD code <sup>a</sup>	No. of					
	Heart recipients		Kidney recipients		Total	
	Observed	Expected	Observed	Expected	Observed	Expected
151 (gastric cancer)	4	5.98	28	26.88	32	32.86
153 (colon cancer)	20	12.90	55	49.37	75	62.27
154 (rectal cancer)	2	8.55	13	32.95	15	41.50

<sup>a</sup> ICD, International Classification of Diseases.

Table 3 Incidence of rectal cancer

Posttransplant yr	Observed	Expected
1	6	10.51
2	2	8.30
3	0	6.57
4	0	5.08
5+	7	11.04

Table 4 Incidence of rectal cancer related to drug therapy

	Observed	Expected	%
Heart recipients			
Cyclosporine, azathioprine, and steroids	2	7.16	27.9%
Other	0	1.37	—
Kidney recipients			
Cyclosporine, azathioprine, and steroids	4	15.15	26.4%
Other	9	17.82	50.5%

leukemia virus-induced lymphoma in mice (11). In each of these, there is immune promotion of the premalignant hyperplastic lesions, leading to cancer. For carcinogen-induced colon and rectal carcinoma in mice and rats, compelling evidence has recently been published supporting the role of immune promotion of chemically induced carcinogenesis (12–18).

In mice (12), a significant positive linear regression relationship was found between the numerical distribution of GALT and the numerical distribution of tumors along the length of the large bowel. The distal third of the large bowel contained 98% of the adenocarcinomas, the middle third contained 2%, and no tumors were found in the proximal third of the large bowel. This suggested that the lymphoid follicles in the proximal and mid-colon of mice have greatly reduced tumor promotion potential compared to lymphoid nodules in the distal colon and rectum.

Hyperplastic epithelial cells with increased proliferation are found in intimate association with lymphoid tissue in the colon and rectum in healthy animals, sites that are susceptible to carcinogens. A 10-fold increase in crypt epithelial cell proliferation has been described (19) in organ culture of fetal human small intestine explants in which a cell-mediated immune response has been elicited. Activation of T cells in the *lamina propria* by the lectin pokeweed mitogen or mitogenic monoclonal anti-CD3 antibodies produces crypt cell hyperplasia.

In humans, cancer of the rectum shows the highest incidence of cancers in the large bowel (20–23). The density of lymphoid follicles in the large bowel is greatest in the rectum, regardless of age and sex (24).

An analysis (25) of the lymphoglandular complexes in the human colon and rectum has revealed some important differences that lend support to the possibility that there is a different intensity of immune function in the rectum compared to the colon, confirming the finding (24) that lymphoglandular complexes are most frequent in the rectum, as recognized in 1935 by Steindl (26), who coined the term “rectal tonsil.” Such complexes contain multiple germinal centers more frequently than the colon complexes in which approximately 1% have germinal centers. A “dome” variant of lymphoglandular complexes is

most frequent in the rectum and is covered by the specialized M epithelium. This lacks microvilli and contains vesicles indicating transport of particulate matter into the lymph follicles (27–30). In the proximal colon, approximately 1–2 M cells are present for every 20 colonic epithelial cells, whereas in the rectum, the relative frequency of M cells is 4× greater.

Thus, in the rectum, there is an increased capacity for antigen transport into a dense population of lymph follicles with a higher percentage of germinal centers, compared to the colon. The presence of suppressor cells (31, 32) ensures that there is a muted immune response to fecal antigens, concentrated in the rectum compared with the colon. Prehn (33) has shown quite conclusively that immune promotion of tumors induced by chemical carcinogens is by a weak immune response of the host. Abolition of such a weak immune promotion of oncogenesis by chronic immunosuppression would explain the highly significant reduction of the incidence of rectal cancer that we report.

The absence of any effect of immunosuppression on the incidence of gastric cancer would suggest that immunopromotion is not operating in the development of this cancer. The slight increase in colon cancer that we observe would parallel the findings in mice that promotion of oncogenesis is not seen in the proximal or mid-colon and could be interpreted as secondary to suppression of immune surveillance. An alternative explanation is that there is perturbation of immune reactions by cyclosporine in colon GALT to levels that promote oncogenesis in colon cancer. Whiteside *et al.* (34) have also noted perturbation of lymphocyte function and numbers in 96 patients serially monitored after orthotopic liver transplantation, treated by cyclosporine or FK506. Activated lymphocytes were found despite the use of these drugs. In rats receiving cyclosporine, striking changes were observed in GALT (35). A significant increase in colon cancers (36) was seen in animals fed a basal diet containing cyclosporine, exposed to a single injection of a carcinogen. The authors postulate that cyclosporine promotes the develop-

ment of colon cancer in rats through complex interactions between the markedly perturbed lymphoid cells and adjacent epithelium.

In conclusion, a highly significant reduction of the incidence of rectal cancer has been shown in a large cohort of men and women chronically immunosuppressed after organ transplantation. This is in comparison with gastric cancer frequency close to expected or background rates, and colon cancer frequency slightly higher than expected. An explanation for these different results would suggest that there is a different impact of immunosuppression on the GALT function in the rectum, colon, and stomach. The strongest effect seen in heart recipients would suggest a dose response secondary to the more intense immunosuppression received by such patients, and the more marked reduction in incidence seen when all such drugs are used would suggest synergism or may reflect higher total doses. The fact that there is a greater reduction in rectal cancer in men would add the possibility of hormonal differences being important. What emerges is the recognition that there exist diverse and complex influences. An analysis of immune function in GALT may shed important light on the net effect of such function in the development of tumors in the stomach, colon, and rectum in immunosuppressed patients.

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