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Promotional Role of Lymphoid Nodules in Colorectal Cancer: Implications for Endoscopic Screening and Prevention

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Abstract: This report examines the anatomical distribution of colorectal cancer CRC in the human large bowel. The findings indicate the high occurrence of cancer in the rectum. The reason for the high incidence of rectal cancer is explored. Published data were compiled and analyzed to correlate the high occurrence of CRC in the human rectum to the high occurrence of lymphoid nodules (LNs). Histopathologic classification and distribution of CRC types was reviewed. Statistical findings reveal a significant ($p < 0.01$) positive relationship between number of LNs and number of CRCs. Histopathological findings indicate that LNs promote epithelial hyperplasia and a nonpolyploid pathway of cancer development especially in the rectum.The findings of a 7 to 8 fold higher density of rectal cancer per cm length in the human rectum compared to the other segments of the large bowel emphasize the importance of careful endoscope screening for the detection of nonpolyploid rectal cancers. Review of human and rat literature suggests that drugs that suppress the immune system and that aspirin, an anti-inflammatory agent,may work to reduce risk of CRC *via* their effect on lymphoid nodules.

Keywords: Colorectal cancer, lymphoid nodules, CRC promotion, CRC prevention, rectal cancer, endoscopy.

1. INTRODUCTION

This report examines: the anatomical distribution of CRCs and summarizes evidence that lymphoid nodules promote de novo CRC in rats and in the rectum of humans. Implications for CRC endoscopic screening and for CRC prevention are discussed.

2. ANATOMIC DISTRIBUTION OF HUMAN COLORECTAL CANCERS

CRC is not uniformly distributed through the large bowel as summarized in Table **1** [1-26]. The right or proximal side (consisting of cecum, ascending and transverse sections) is affected by cancer less frequently than the left or distal side (consisting of descending, sigmoid and rectum sections). On average, the left side is demonstrated to have more than twice the number of cancers as the right side.

The CRC incidence values reported in Table **1** are the general values reported in each study. Factors such as age, gender, ethnicity, or time of study are not factored into the incidence values reported in Table **1**. Table **1** indicates the study site of each report as well as the rectal incidence values, in parenthesis, from those studies where reported. Available data on study sample size (number in study) is also reported in Table **1**.

Fig. (**1**) summarizes the date in Table **1** and illustrates difference in the distribution of CRC in the large bowel. The mean ± SE percent of CRCs in each location is: Right 27.84 ± 1.48, Left 71.97 ± 1.51, Rectum 39.60 ± 2.73, Left minus Rectum 31.96 ± 1.99. An analysis of variance of these data followed by a multiple range test indicates the left side is about two fold significantly higher ($p < 0.001$) than the other locations. The rectum is significantly higher than either the Right or the Left minus the Rectum ($p > 0.001$).

These CRC distribution data, when expressed per cm length of each location, reveal a telling fact. Given the average lengths of large bowel segments are: Right 67 cm, Left 78 cm, Rectum 12 cm and Left minus rectum 66 cm and dividing by the mean percent of tumors in each of these four segments by the cm length values gives the percent of all CRC's per cm along the length of the large bowel. The percent values obtained by this procedure, as illustrated in Fig. (**2**), are: Right 0.42%/cm, Left 0.92%/cm, Rectum 3.30%/cm, Left minus rectum 0.48%/cm. Thus one can expect 6.9 to 7.8 times more cancers per cm length of rectum than elsewhere in the large bowel. This finding emphasizes the importance of careful endoscopic screening of the rectum for detection of CRCs.

3. CONGRUENCE IN DISTRIBUTION OF CRC AND LYMPHOID NODULES (LN's) IN THE LARGE BOWEL

This section of the report shows research results from large bowel carcinogen induced CRC in animal models that has led to a more complete understanding of CRC distribution in humans.

Fig. (**3**), from Hardman and Cameron, summarizes results of three past studies on the CRC distribution in the large bowel following injection of a CRC inducing carcinogen in rats [27]. In these studies, a large bowel carcinogen was administered followed by a period of time before sacrifice. The occurrence of large intestinal lesions was scored as percent of the distance from the anus to the ileum. Histopathology of each lesion was done to confirm if the lesion was

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Table 1. Distribution of Colorectal Cancers Expressed as Percent of Total Number of Right and Left Sided Cancers. Rectal Subsite Values Reported in Parentheses

Right	Left (Rectum)	Study Site	Reference	Year	Number in Study
40	60 (15)	Los Angeles	Morgenstern and Lee [1]	1978	1,009
27	73 (34)	New York	Chattar-Coat *et al.* [2]	1998	180
39	61 (28)	New York	Fleshner *et al.* [3]	1989	922
39	61	US	Shellnut *et al.* [4]	2010	6,925
42	58 (29)	US	Cooper *et al.* [5]	1995	75,266
36	64 (41)	US	Qing *et al.* [6]	2009	690
33	67 (48)	US	Wu *et al.* [7]	2004	336,798
31	63 (38)	Ontario, Canada	Cancer Facts [8]	2010	37,580
23	77 (37)	Brazil	Bromberg [9]	2002	320
28	72 (29)	West India	McFarlane *et al.* [10]	2004	132
31	69	UK	Gomez *et al.* [11]	2004	771
32	68 (37)	UK	UK@Cancer Stats	2010	62,896
28	72	N. Ireland	Crerand *et al.* [12]	2001	5,153
33	67 (33)	N. Ireland	McCallion *et al.* [13]	2001	4,931
33	67 (39)	Scandinavia	Eide [15]	1986	
23	77 (38)	Netherlands	van Rossum *et al.* [14]	2008	185
31	69 (26)	Netherlands	Mensink *et al.* [16]	2002	642
26	74 (33)	Italy	Ponz de Leon *et al.* [17]	2004	2,462
17	83 (44)	Nigeria	Abdulkareem *et al.* [18]	2009	399
9	91 (74)	Guinea	Odigie *et al.* [19]	2009	262
14	86 (55)	Iran	Nikshoar *et al.* [20]	2006	2,107
24	76 (67)	India	Deo *et al.* [21]	2001	91
26	74	India	Peedikayil *et al.* [22]	2009	220
36	64 (36)	New Zealand	Jass [23]	1991	15,395
25	75 (24)	Japan	Sakamoto *et al.* [24]	2006	565
34	66 (27)	Japan	Goto [25]	2006	14,817
24	76	Japan	Fu *et al.* [26]	2005	1,324
26	74 (54)	China	Qing *et al.* [6]	2009	870
11	89	China	Leng *et al.* [27]	2010	4,450
22	78 (51)	Taiwan	Shieh *et al.* [29]	1990	1,198
20	80 (53)	Korea	Kim *et al.* [28]	2000	4,129

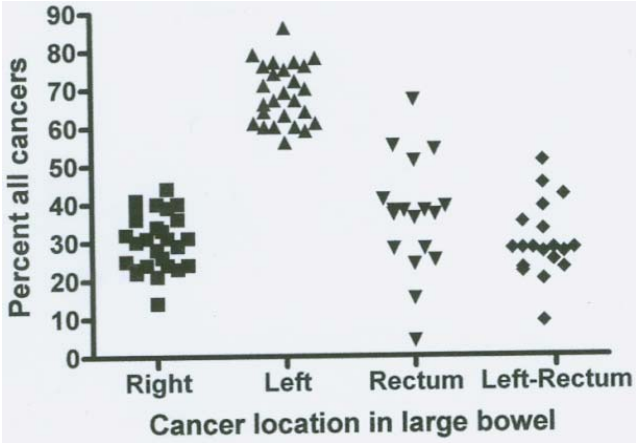

Fig. (1). Graph summarizing distribution of percent of all CRC's located in different locations in the large bowel (data from Table **1**). Statistical analysis reveals the incidence of CRC is significantly higher in the left side of the large bowel than other locations but no other significant differences.

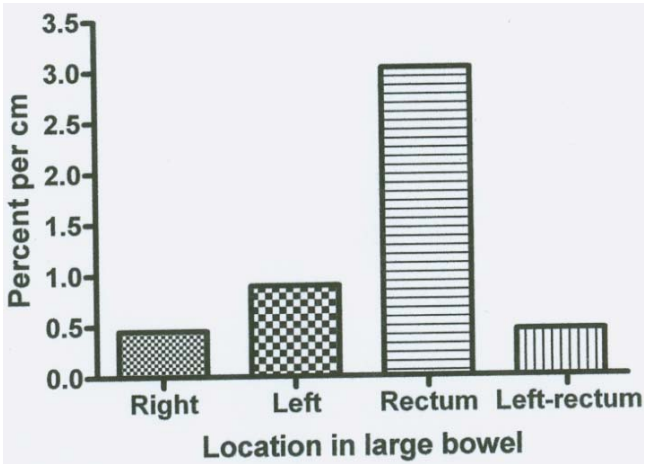

Fig. (2). Bar graph of mean incidence of CRC's (from Table **1**) expressed per cm length of each large bowel section. This graph illustrates there are 7-8 times more CRC per cm of rectum than elsewhere in the large bowel.

a carcinoma or adenoma. The data in Fig. (**3**) is limited to carcinoma distribution [27-30]. The results of each of the three reported studies reveal a trimodel distribution of CRC along the length of the rat large bowel.

What could be responsible for this trimodel distribution of CRC? The study of Nauss *et al*. reported on the distribution of: carcinomas (polyploid and sessile types), adenomas and aggregates of lymphoid nodules (ALN) along the length of the rat large bowel [28]. A linear regression analysis of their data was reported by Cameron *et al.* [33]. The distribution of ALN scored at the time of sacrifice of the DMH-treated rats, was significantly correlated with the distribution of the more sessile cancers but was not significantly correlated with the less numerous polyploid cancers or adenomas. The significant correlation between carcinogen (DMH) induced CRC and the location of ALN in rats was confirmed by Hardman and Cameron 1994 [30]. Carter *et al.* also reported a significant positive linear regression relationship between the numerical distribution of LN and the numerical distribution of CRC in the large bowel of DMH treated mice [31].

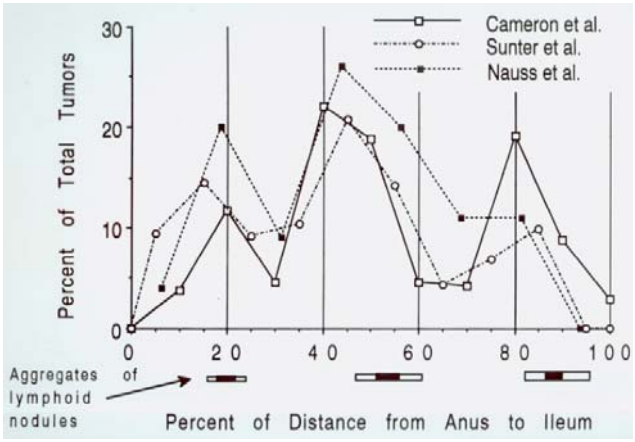

Fig. (3). Graphs the percent of the total number of CRC's found in rats treated with a large bowel carcinogen as a function of percent of distance from anus to illeum. The data are form three previous experiments [28-30]. The location of aggregates of lymphoid nodules (ALN) of 20 non-colon carcinogen treated rats is indicated by bars along the horizontal axis of the graph. No solitary LN's were found between the ALN's. This graph shows correlation in occurrences of CRC and location of ALN. This correlation is significant (see text). Graph reproduced from reference [27] with permission of Oxford University Press.

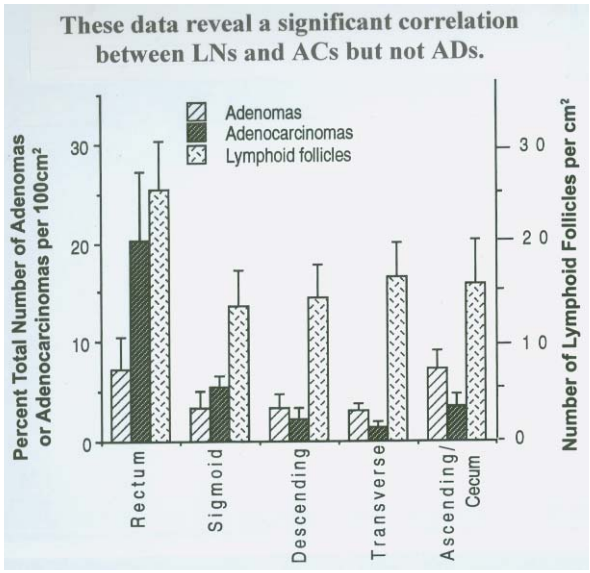

Fig. (4). The anatomic distribution of adenomas (AD) adenocarcinomas (AC) and lymphoid nodules (LN's) in the human large bowel. The results from multiple sources were gathered and evaluated [14, 42]. The findings are expressed per cm^2 of macroscopic surface. The number of LN's and AC's but not AD's was significantly higher in the rectum than elsewhere in the large bowel. The linear regression of the five bowel segments reveals significant correlation between LN's and AC's but not between LN's and AD's.

There is also evidence in support of a significant correlation between the numerical distribution of CRC and of LN in humans. The data in Fig. (**4**) gives information on the nu-

merical distribution of adenomas, CRC [14,32] and LN's [33] in various segments along the length of the large bowel. Linear regression analysis of the mean values from each bowel segment indicates a significant linear correlation between numerical density of LN and CRC ($p < 0.05$) but not of adenomas ($p > 0.05$).

As reported above there is a 7-8 fold higher incidence of CRC per cm length in the human rectum than elsewhere in the large bowel. A careful study of number of LN along the length of the rectum and the lower segment of the sigmoid colon in five human cadavers [34] was correlated with the incidence of CRC in the same region of the large bowel in 50 patients diagnosed with CRC in the rectum and lower segment of the sigmoid colon [35]. Endoscopic measurements indicated the location of each CRC up to a distance of 22 cm above the anal verge. Fig. (**5**) summarizes the LN and CRC results of this study. Linear regression analysis of the number of LN's vs. the incidence of CRC indicated a significant linear correlation ($p < 0.01$).

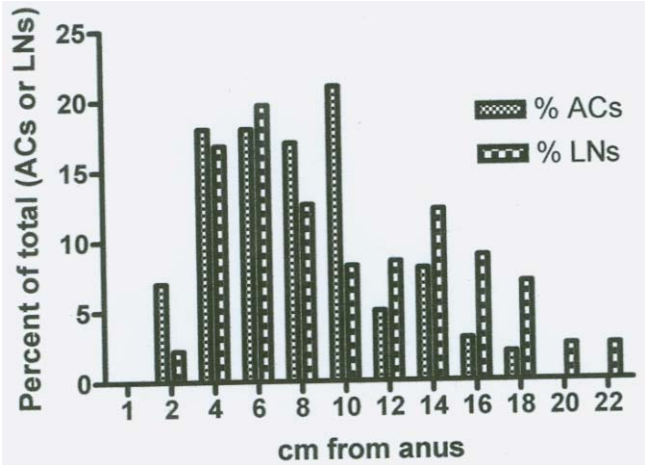

Fig. (5). Graph of the distribution of LN's and cancers at distances from the anal verge of humans. LN's and cancers occurred most frequently between 3.5 and 10 cm form the anal verge. Linear regression analysis reveals a significant correlation, $p< 0.01$, between cancer and LN frequency [38].

The results of these and other human studies give further credence to the conclusions derived from the animal studies by demonstrating that a significant positive linear relationship between numerical density of LN's and incidence of CRC occur in both animal models and humans.

4. PROMOTIONAL ROLE OF LYMPHOID NODULES (LN's) IN THE FORMATION OF CRC

That LN's have a promotion role in formation of CRC in DMH-treated rats is evident from the research of Hardman and Cameron [30]. A summary of their finding follows: The colonic crypt height and proliferative zone in crypts located over the aggregates of LN was significantly higher than in crypts located away from LN. This finding occurred in both DMH and non-DMH treated rats. Transforming growth factor alpha, a mitogenic factor, was found in the proliferation zone cells in crypts located over LN but not in crypts located away from LN. Crypts immediately adjacent to LN in humans demonstrate these same morphological features [36-40].

Histological sections taken through the ALN of DMH-treated rats showed that 32% of them revealed presence of microscopic carcinoma either within or immediately adjacent to ALN (examples in Fig. **6**) but in the same rats no microscopic carcinomas were observed in sections taken away from the ALN [27]. None of these microscopic cancers showed evidence of an adenomatous precursor nor was there any evidence of a lesion on the surface over the cancer. This observation provides evidence that these endophytic cancers arouse *de novo*.

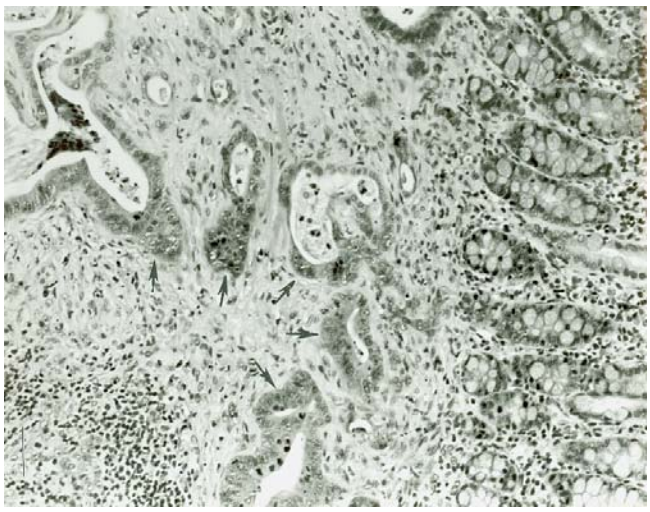

Fig. (6). Histological section of the large bowel wall of a rat treated with a large bowelcarcinogen [28]. Colon crypts are at right of this micrograph and a submucosal lymphoid nodule is at lower left. Arrows point to areas of submucosal carcinoma. The rat was injected with colchicine 3 hours prior to sacrifice to arrest dividing cells at metaphase (dark condensed chromatin area in cells). Notice that submucosal carcinoma cells closest to the nodule are taller and were more basophilic than the carcinoma cells further away from the lymphoid nodule.

Because ALN are consistently found in the same three sites along the length of the large bowel in rats that have not received the DMH carcinogen and because few LN occur elsewhere in the large bowel of the rats it is concluded that LN associated with CRC's were present before CRC developed and that the LN did not arise as an immune response to the CRC. This conclusion suggests that factors associated with LN are promotional to CRC in rats. Thus the specific anatomical location of LN's predetermines the distribution of CRC along the length of the large bowel of carcinogen-treated rats and humans. This is not meant to imply that there is not an immunological reaction to the presence of a neoplasm [41].

The published reports from studies on carcinogen-induced CRC in rats and mice suggests a promotional role for LN's in CRC carcinogenesis [27-31, 36, 37].

What is the evidence that LN's promote formation of nonpolyploid or endophytic cancers?

As mentioned above Cameron *et al.* [33], using data published by Nauss *et al.* [31] on the distribution of polyploid and sessile-nonpolyploid cancers and of aggregates of LN's in DMH treated rat, revealed a significant linear relationship between number of sessile cancers and number of LN's but

not of the number of the less frequently occurring polyploid cancer. Thus the nonpolyploid cancers but not polyploid cancers occurred significantly more frequently in regions of LN's than in regions away from LN's.

In humans a histopathological analysis of all nonpolyploid and polyploid cancers found presence of an LN in 36% of nonpolyploid neoplasias but in only 9% of polyploid neoplasias (Rubio 2000) [45]. Fu *et al.* [26] reported on the incidence and on the location of LN's of early colorectal neoplasms in 1,031 humans. Histological examination revealed a 3.2 fold significantly higher incidence of LN's in the left vs. the right large bowel. They also found that 80% of nonprotruding early CRC's associated with LN's were located under the muscularis mucosa (submucosal) while only 36% of protruding early CRCs associated with LN's were located over or across the muscularis mucosa (intramucosal). Thus Fu *et al.* present evidence in support of a significant correlation between the incidence of LN's and invasive tendencies of early CRC's in humans. Kobayaski *et al.* [46] have recently reviewed this subject. Their findings suggest LN are promotional to formation of the nonpolyploid-sessile-flat and depressed type cancers. Just how many of the CRC's in humans are of the nonpolyploid type and how many have developed by a nonadenomatous (de novo) pathway?

Table **2** summarizes literature on the reported incidence of nonpolyploid CRC's in humans [9, 23, 44-51]. The proportion of nonpolyploid CRC's ranges from 6.8 to 80% with a mean of 31%. Goto *et al.* [25] attributes this wide range to differences in selection of subjects, sample size and the definition of nonpolyploid de novo cancers. Goto defines de novo cancers by the following criteria: absence of adenomatous component, all lateral margins covered by mucosa and a nonpolypoid or sessile growth pattern. Using these criteria Goto *et al.* [25], reported the incidence of de novo cancers in the following large bowel segments: Right 21%, Left-rectum 18%, and Rectum 32%. Expressing these data as percent of de novo cancers per cm length gives the following value: Right 0.31%, Left-rectum 0.272%, Rectum 2.58%. Expressed in this way indicates 8.3 to 9.6 times more de novo cancers per cm length in the rectum compared to the rest of the large bowel. This large difference emphasizes the importance of careful endoscopic screening for detection of de novo type cancers in the rectum.

Expressing human LN incidence data from Fig. (**4**) per cm length in the rectum compared to the rest of the large bowel indicates 5.2 times more LN's per cm in the rectum compared to the rest of the large bowel. Taking the rectal de novo cancer incidence data of Goto *et al*. and LN incidence data together suggests a promotional role of LN in the formation of de novo cancers.

A promotion effect of LN's on cancer development is illustrated in Fig. (**6**).

This histological section is from a de novo cancer from a rat treated with the large bowel carcinogen DMH [27]. The rat was injected with colchicine 3 hours before sacrifice. Colchicine arrests mitotic cells at metaphase and allows easy identification of areas of high cell proliferation in the histological section. Colon crypts are shown at the top of the figure and a submucosal lymphoid nodule is present at the bottom right part of the figure. The arrows point to submucosal carcinoma adjacent to the LN. Notice that carcinoma cells closer to the LN are larger and were more basophilic than those carcinoma cells further away from the LN. Also notice the high incidence of metaphase figures in the carcinoma cells located closer to the LN. These observations are interpreted to indicate that one or more paracrine LN derived growth factors is responsible for the promotion of the hyperplastic response on the carcinoma cells.

Implications for CRC Endoscopic Screening and for CRC Prevention

The finding presented in this report indicates that the first 14 to 19 cm of rectum up from the anus in humans is a site with an especially high rate of occurrence of cancer. The finding also indicates that high frequency of cancers that occur in the rectum can be linked to the high numerical density of LN's and to the promotional role of LN's on forma-

Table 2. Nonpolyploid Colorectal Cancers Expressed as Percent of Total Number

Percent	Study site	Reference	Year	Number in study
15%	Germany	Kiesslich *et al.* [47]	2007	100
40%	France	Bedenne *et al.* [48]	1992	1,630
23%	Japan	Goto *et al.* [25]	2006	14,817
33%	Japan	Matsuda *et al.* [49]	2010	6,638
>30%	Taiwan	Chen *et al.* [50]	2003	960
80%	Japan	Shimoda *et al.* [51]	1989	146
>30%	UK	Rembacken *et al.* [52]	2000	1,000
46%	Brasil	Bromberg [9]	2002	320
22%	Germany	Stolte and Bethke [53]	1995	150
6.8%	Sweden	Tsuda *et al.* [54]	2002	973
9%	U.S.	Soetikno *et al.* [55]	2008	1,059

tion of de novo cancers. The endoscopic detection of non-polyploid/de novo CRCs presents a challenge. The challenge is to become proficient in endoscopic recognition of de novo cancers in order to remove them and to reduce CRC mortality rate. Use of new endoscopic techniques such as high magnification chromoscopic endoscopy (H-MCE) holds promise for distinguishing de novo (neoplastic) lesions from non-neoplastic lesions [53-57].

Given a promotional role of LN's on formation of CRC suggest that immunosuppressive measures might reduce the promotional effects of lymphoid nodules in the large bowel. Also given the high density of LN's in the rectum of human and their hyperplastic promotional role in CRC development one might predict that chronic administration of immunosuppressive drugs might selectively reduce risk of rectal cancer vs. nonrectal coloncancer that occurs elsewhere in the large bowel. Stewart *et al.* have indeed found that chronically immunosuppressed people do demonstrate a significant and selective reduction in incidence of rectal cancer (Table **3**) [58]. It seems possible that long term use of immunosuppressive drugs may have suppressed CRC incidence *via* its anti-inflammatory action. In this regard it has been reported that regular use of aspirin, an anti-inflammatory drug, also reduces risk of CRC in humans and in animal models [59, 60]. It is suggested that effective CRC prevention strategies might specifically target suppression of the CRC-promotional activity of large bowel lymphoid nodules.

Table 3. Incidence of Gastric, Colon and Rectal Cancer in 73,076 Heart or Kidney Transplant Recipients[a] (Stewart, T., *et al.*, Clin. Cancer Res. 3:51, 1997)

	Observed	Expected
gastric	32[b]	33
colon	75[b]	62
rectal	15[c]	42

[a]Immunosuppression treatment drugs: cyclosporine, azathioprine, steroids.
[b]Not significantly different from expected.
[c]Significantly different from expected and the protection was greater in men than in women.

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CONFLICT OF INTEREST

None Declared.

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