Colonic cell proliferation in two different ethnic groups with contrasting incidence of colon cancer: is there a difference in carcinogenesis?

A van't Hof, K Gilissen, R J Cohen, L Taylor, Z Haffajee, A L Thornley, I Segal

Abstract

Most studies on colorectal carcinogenesis suggest a field defect, preceding overt development of cancer. The low incidence of adenomatous polyps in the African population, however, suggests that there may be an alternative route for cancer development. The aim of the study was to discover if the difference in incidence of colorectal cancer in Africans compared with the white population is reflected in a different pattern of cell proliferation. Histological normal mucosa from 30 patients (15 white South African (W), 15 South African Africans (A)) with confirmed colon cancer were examined. Proliferating cells were detected using the Ki-67 antigen. In addition, cell proliferation data were obtained, from 30 age matched controls (15 Africans, 15 white South Africans), without colorectal disease. The African controls were significantly younger (mean (SD) (A: 42 (20), W: 66 (13), $p < 0.05$)) than the white controls. The second control group had a significantly higher mean (SD) total labelling index (W: 11 (3), A: 6 (4), $p < 0.05$). In addition the proliferative pattern of the white group without evidence of colorectal cancer showed a comparatively large amount of dividing cells in compartment 2, compared with African controls (mean (SD) (W: 21 (8), A: 9 (8), $p < 0.05$)). Mucosa from Africans with cancer showed a proliferative pattern with the same increased total labelling index (A: 15 (5), W: 16 (6), $p = \text{NS}$, phase II proliferative lesion) and an even more pronounced upward expansion (phase I proliferative lesion) compared with white cancer patients. This suggests that the mechanism of colorectal carcinogenesis is similar in Africans and the white population. The lack of clinical evidence of the adenoma-carcinoma sequence, and the incidence of cancer at a comparatively young age in Africans may be explained by the fact that colorectal cancer in this ethnic group behaves more aggressively and that adenomatous polyps are rapidly converted into overt cancer before detection.

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Keywords: colonic cell proliferation, colonic cancer.

The exact mechanism of colorectal carcinogenesis is controversial. Some authors support

the adenoma-carcinoma sequence,¹⁻⁶ while others state that 'de novo' development of colorectal cancer is not unusual.⁷⁻⁹

It is known that colorectal cancer in Africans is uncommon and that adenomatous polyps are rare.¹⁰ During a 12 year period (1956-1968), only six adenomatous polyps were reported in a review of surgical specimens in a 2000 bed hospital and no polyps were reported in a series of 1000 necropsy examinations, in which the bowel had been routinely opened and inspected.¹¹ In a later study (1969-1978), only six (3%) adenomatous polyps were found in 205 African patients. It was also found that most cancers were unrelated to polyps.¹² These findings suggest that in Africans, colorectal cancer may have a different genesis to that of the Westernised population.

Data from cell kinetic parameters can give insight into the mechanism of colorectal carcinogenesis. It was suggested that hyperplastic polyps are not related to the histogenetic process of colorectal cancer, because there was no significant difference in cell proliferation in comparison with normal mucosa.¹⁵ Deschner *et al* found that the proliferative pattern in crypts of mice and rats were different. It was suggested that the direction of the shift in the major zone of proliferation is related to the type of lesion present in the colonic mucosa. Downward migration seemed to be related with intramucosal formed cancers, and upward migration with adenomatous polyps.⁸

This study compares the proliferative pattern of histologically normal mucosa from African and white patients, with and without colonic cancer. The aim of the study was to assess if the low incidence of colorectal adenomatous polyps and cancer in Africans is reflected in a different pattern of cell proliferation.

Methods

SPECIMENS

Specimens were obtained from 30 patients with confirmed colonic carcinoma, selected from the index files of the department of histopathology at the University of Witwatersrand. Only normal appearing colonic mucosa, obtained from the tumour free resection margins, was examined, and mucosa within a distance of 2 cm from the tumour was excluded. The surgical specimens were routinely fixed in

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TABLE 1 Demographic and colonic cell proliferation data of Africans and white patients with colorectal cancer

	Africans	White patients
Number	15	15
Age (y) (mean (SD)) (range)	48 (18) (27-79)	70 (12) (44-86)*
Sex	9 M, 6 F	8 M, 6 F
Distance from tumour (mean (SD))	10 (8) (n=12)	12 (9) (n=11)†
Dukes's classification		
A	0	1
B	5	4
C	8	9
D	2	1
Differentiation		
well	4	1
moderate	9	12
poor	2	2
Location		
caecum	3	2
ascending	—	1
transverse	—	2
descending	1	—
sigmoid	5	3
rectum	4	2
unknown	2	5
No of crypts counted/patient (mean (SD)) (range)	9 (3) (6-15)	9 (2) (6-12)
Positive no of cells/crypt (mean (SD)) (range)	23 (9) (6-42)	24 (9) (13-39)†
Labelling index (×100) (mean (SD)) (range)	15 (5) (6-25)	16 (6) (8-27)†
Labelling index (×100) (mean (SD))		
compartment 1	28 (8)	34 (14)†
compartment 2	29 (10)	31 (12)†
compartment 3	14 (8)	13 (6)†
compartment 4+5	4 (6)	2 (2)†

*p<0.05; †p=NS (analysis of variance); ‡p=NS (Mann-Whitney).

formalin and processed. Sections of 4 microns were cut and dried overnight to ensure adequate adhesion before staining.

In addition, biopsy specimens were obtained from 30 age matched control patients (15 Africans, 15 white patients), without colorectal disease. All patients underwent endoscopy between 9 00 am and 2 00 pm, after whole gut irrigation. Patients signed an informed consent form before the procedure. Biopsy specimens were taken at a mean of 20 cm (Africans) and of 26 cm (white patients) from the anal ring. Immediately after the biopsy, the specimens were coded and orientated mucosal side up on filter paper and formalin fixed. Four micro thick sections were cut from paraffin wax blocks. Patients with histologically abnormal mucosa were excluded.

IMMUNOHISTOCHEMISTRY

Proliferating cells were detected, using the MIB1 antibody (DIANOVA GmbH). The MIB1 antibody reacts with the Ki-67 nuclear antigen and has the advantage that it can be used in routinely processed, formalin fixed, paraffin wax sections.¹³

Sections were dewaxed, hydrated, and trypsinised (0.1% trypsin) for 15 minutes at 37°C. While in a citrate buffer (pH 6.0), slides were exposed to microwave irradiation for a period of nine minutes (three times three minutes). Endogenous peroxidase was blocked, using 0.3% H₂O₂ in methanol, for 20 minutes. After washing in phosphate buffered saline the sections were covered with normal horse serum for 20 minutes. The slides were then incubated in the primary antibody (MIB1, dilution 1:10) for 60 minutes at 37°C. Antibody detection was made with an avidin-biotin horseradish peroxidase complex (VECTASTAIN, ABC) with diaminobenzidine as the chromogen. The sections were lightly counterstained with haematoxylin.

QUANTIFICATION

Only whole length, longitudinal crypts were selected. These were defined as crypts with the muscularis mucosa at the bottom and the surface at the top. Scoring of nuclei was done manually, by only one observer, with the use of a light microscope (×400). Nuclei were counted as positive if any nuclear staining was present.

ANALYSIS

The parameters used were: the mean number of labelled nuclei per crypt, the mean number of total nuclei per crypt, and the labelling index, which is the ratio of labelled (MIB1 positive) to the total (MIB1 positive+MIB1 negative) number of nuclei. In addition, the crypt was divided into five equally sized compartments (from base to surface) and the number of (labelled) nuclei in each compartment was calculated. This permitted the calculation of a labelling index for each of the five compartments.

Statistical analysis

One way analysis of variance was used for comparison of the mean values of labelling indices. When data were not normally distributed, the Mann-Whitney test was used.

Results

PATIENTS WITH COLORECTAL CANCER

Thirty patients (15 South African Africans, 15 South African whites), were selected. The African group was significantly younger. In the Africans four patients had well differentiated tumours compared with one in the white group. For seven patients the exact distance of the mucosa to the tumour was not known (Table I).

PATIENTS WITHOUT COLORECTAL DISEASE

There was no statistical significant difference in age between patients with colorectal cancer and controls from the same ethnic group. The indications for endoscopy included microcytic anaemia, abdominal pain, diarrhoea, and perirectal bleeding. In one white patient, we found evidence of angiodysplasia and four other patients (two Africans, two white patients) had diverticula. On histological examination one African patient had melanosis coli and another showed an ovum of schistosoma in the section. These abnormalities were thought not to influence the cell proliferation data (Table II).

QUANTITATIVE RESULTS

Patients with colon cancer

The total number of labelled nuclei and the total labelling index do not differ significantly between the two ethnic groups. Although there is a trend towards a higher mean labelling

TABLE II Demographic and colonic cell proliferation data of Africans and white patients without colorectal cancer

	Africans	White patients
Number	15	15
Age (y) (mean (SD)) (range)	42 (20) (16–75)	66 (13) (30–82)*
Sex	7 M, 8 F	4 M, 11 F
Indication for endoscopy		
anaemia	8	2
abdominal pain	1	7
constipation	0	1
diarrhoea	1	3
loss of weight	1	0
perirectal bleeding	4	1
unknown	0	1
Macroscopic pathology		
none	13	12
angiodyplasia	0	1
diverticula	2	2
Microscopic pathology		
none	13	15
melanosis coli	1	0
schistosomiasis	1	0
Time of biopsy	10 15–13 00	08 55–14 15
Distance from anal ring (cm) (mean (SD))	20 (6)	26 (4)†
No of crypts counted/patient (mean (SD)) (range)	9 (3) (5–15)	9 (3) (5–15)
Positive no of cells/crypt (mean (SD)) (range)	7 (6) (3–25)	13 (4) (8–18)*
Labelling index (×100) (mean (SD)) (range)	6 (4) (2–18)	11 (3) (7–17)*
Labelling index (×100) (mean (SD))		
compartment 1	15 (7)	23 (6)*
compartment 2	9 (8)	21 (8)*
compartment 3	4 (6)	11 (6)*
compartment 4+5	0 (1)	1 (1)‡

* $p < 0.05$; † $p = \text{NS}$ (analysis of variance); ‡ $p = \text{NS}$ (Mann-Whitney).

index of the upper crypt compartments in the mucosa from Africans, it is not statistically significant (Table I, Fig 1).

In a subgroup of 23 patients (12 Africans, 11 white patients) in which the distance of the mucosa to the tumour was known, the total labelling index of mucosa within a distance of 5 cm from the tumour, was 19 (+5) for the African patients and 27 (+2) for the white patients. Labelling indices from mucosa located more than 5 cm away from the carcinoma was 12 (+4) and 15 (+4) respectively, which is significantly lower ($p < 0.05$) (Table III). This finding is in agreement with previous studies, which report a negative correlation between the distance from the tumour and the cell proliferation rate.^{9 14}

Patients without colorectal disease

Table II summarises epithelial cell proliferation variables for patients without colorectal cancer. The white patients had a significantly

Figure 1: Comparison of labelling index (mean (SD)) in each crypt compartment between the two ethnic groups with colon cancer (compartment 1 is located at the base of the crypt, compartment 5 at the surface).

higher mean total labelling index than Africans (phase II proliferative lesion). In addition, the proliferative pattern of white patients without evidence of colorectal cancer, showed a comparatively large amount of dividing cells in compartment 2, compared with the African controls (phase I proliferative lesion) (Fig 2). This is in agreement with the results from other studies.^{15–17} They also showed that patients at increased risk of colon cancer may show a proliferative pattern of the mucosa, which is characterised by phase I and phase II proliferative lesions, in the absence of any colorectal abnormality.

Discussion

The results show that white controls had a significantly higher mean total labelling index than African controls. In addition the proliferative pattern of white controls without evidence of colorectal cancer showed a comparatively large amount of dividing cells in compartment 2, compared with African controls. There was a significant difference in age between white and African controls. Our calculations (Table IV) show, however, that, although there is a trend toward a higher rate of cell proliferation with age, it is not statistically significant.

Much information about colorectal carcinogenesis comes from studies concerning cell proliferation. In 1973, Lipkin described phase I and phase II proliferative lesions in the mucosa from patients at increased risk of colorectal cancer.³ He suggested that neoplastic lesions develop in stages: the adenoma-carcinoma sequence. In support of this hypothesis, clinical and histopathological data indeed have shown that most, if not all, malignant colorectal carcinomas arise from pre-existing adenomas.² These studies mainly concern the Westernised populations. In this group, colorectal cancer is the second most common cancer. In this study, cell proliferation data were obtained from a group of South African Africans, in which colorectal cancer is one of the lowest in the world. Moreover, macroscopic adenomatous polyps are seldom seen. This led to the hypothesis that the adenoma-carcinoma sequence does not occur in this ethnic groups.¹² It was suggested that cancer could have arisen de novo or from flat mucosal lesions in apparently normal mucosa. Little is known about the changes in cell proliferation that occur in de novo carcinogenesis or in carcinomas that arise from flat adenomas. Animal studies suggest that the direction of the shift in the major zone of proliferation is related to the type of lesion: downward migration seemed to be related with intramucosal formed cancers, and upward migration with adenomatous polyps.⁸ In humans, however, a

TABLE III Influence of distance from tumour on rate of epithelial cell proliferation

Distance from tumour	< 5 cm	> 5 cm
Labelling index black patients	19 (5)	12 (4)*
Labelling index white patients	27 (2)	15 (4)*

* $p < 0.05$. Data shown as mean (SD).

Figure 2: Comparison of labelling index (mean (SD)) in each crypt compartment between the two ethnic groups without colon cancer (compartment 1 is located at the base of the crypt, compartment 5 at the surface).

downward shift would not be evident as such, as the major zone of cell proliferation is already located at the base of the crypt.¹⁸ Thus, a pattern of cell proliferation would be expected to be found in mucosa from Africans with colon cancer, in which no significant changes in mucosal cell proliferation is present. In this study, however, the mucosa from Africans with colorectal cancer showed an even more pronounced upward shift of the proliferating cells (phase I proliferative lesion) compared with the changes in proliferative pattern, which occur in mucosa from South African white patients with cancer (Fig 3). This suggests that colorectal cancer in Africans is also preceded by adenomas. We reviewed all slides in an attempt to find more evidence of the adenoma-carcinoma sequence in Africans. In two tumours from African patients, it was obvious that the tumour arose from a tubulovillous adenoma. Another African patient had a tubulovillous polyp with severe dysplasia located proximal from the tumour. The white group showed the same percentage of tumours (two of 15, 13%), in which the originating polyp could be found.

If the adenoma-carcinoma sequence were a common event, however, it might be expected that adenomatous polyps would be more common in African patients. This does not seem to occur.¹² A possible mechanism to consider is that colonic cancer may behave more aggressively in this ethnic group. In this

TABLE IV Influence of age on epithelial cell proliferation in patients without colorectal disease

	Young (<67)	Old (≥67)
Africans (n)	11	4
Total labelling index (LI) (×100)	5.3 (3.3)	8.3 (6.7)*
LI compartment 1	13.7 (6.5)	17.8 (8.2)*
LI compartment 2	7.5 (5.6)	14.8 (12.7)*
LI compartment 3	2.8 (3.9)	7.3 (9.2)*
LI compartment 4+5	0.3 (0.5)	0.5 (1.0)*
White patients (n)	6	9
Total labelling index (LI) (×100)	11.3 (2.3)	11.0 (4.0)*
LI compartment 1	24.8 (6.2)	21.6 (5.5)*
LI compartment 2	20.3 (5.0)	21.1 (9.2)*
LI compartment 3	9.2 (4.5)	11.7 (6.6)*
LI compartment 4+5	1.0 (0.9)	0.9 (0.8)*

*p=NS. Data shown as mean (SD).

way, a single precursor lesion, which may only be 1–2 mm in size, may be rapidly replaced by overt cancer, before being detected. In this study it was found that mucosa from Africans with colon cancer showed a more pronounced phase I and phase II proliferative lesions despite a significantly younger age. We suggest that the mucosal changes in Africans progress from a very low risk pattern (as seen in controls) to a high risk pattern in a comparatively short period of time, consistent with a more aggressive tumour behaviour than occurs in white patients. Also other authors suggest a different, possibly more aggressive tumour behaviour in Africans. Michelassi *et al* found different karyotypic characteristics of the neoplastic cells in tumours from Africans.¹⁹ Dayal found that the African race was an independent risk factor, associated with a poor survival from colorectal cancer.²⁰ This study suggests that there are at least two varieties of the adenoma-carcinoma sequence: one in which clearly visible adenomas are gradually replaced by malignant tumour (the most likely mechanism in white patients), and one in which a less easily detectable precursor lesion (flat adenoma) is rapidly replaced by overt cancer (proposed mechanism in Africans). It is suggested that de novo carcinogenesis is a variant of the adenoma-carcinoma sequence. This model is consistent with the hypothesis of Hill *et al*²¹ and Fearon and Vogelstein,² who describe a stepwise model for colorectal

Figure 3: Proliferation pattern of (A) Africans and (B) white patients with colon cancer, compared with controls without colorectal disease. Note the more pronounced phase I and phase II proliferative lesions in the mucosa from Africans with cancer.

tumorigenesis. Intervention at various stages of tumour development, either by (in)activation of certain oncogenes or suppressor genes,² or by the absence or presence of environmental factor A, B, or C,²¹ could explain which variety of adenoma-carcinoma sequence occurs. Studies evaluating the genetic basis of colorectal cancer in low risk communities may uncover important data and assist in elucidating clues to colorectal cancer pathogenesis.

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key topics' category. It should be judged in these terms, of course, as it is not a textbook of paediatric gastroenterology. The authors of the chapters are well recognised names in the community of paediatric gastroenterologists, from North America and from the United Kingdom, with one representative from continental Europe. Predictably, all have undertaken their task competently and successfully.

The success of the publication must depend on the choice of topics included. This is good in the main, but at times somewhat specialist. The generalist who sees children with gastrointestinal problems will find the chapters on oral rehydration solution, constipation, food allergy, inflammatory bowel disease, gastro-oesophageal reflux, recurrent abdominal pain, and gastrointestinal bleeding, of great interest and educational value. The chapter on 'when to transplant the liver in children' fits uncomfortably; it is a very interesting question for the paediatric hepatologist or specialist gastroenterologist but of little relevance to the probable readership of the publication. The chapters on the role of gastrointestinal motility studies and of home parenteral nutrition fall in between, probably. The relevance of the book to a reader will depend on the number of children with these problems they see, and I suspect that the book will be most useful to the general paediatrician and not the general gastroenterologist.

In keeping with the ethos of counting credits, I would rate this book as being worth three credits (assuming that most generalists would probably read six chapters, and perhaps spend half an hour on each). By doing this, they are probably learning more than by earning six credits by listening to the same authors giving lectures on the same topics, and in addition they have the book on their shelves afterwards. Paediatricians should put it on their reading list for next term, as should any general gastroenterologist who sees children.

S P DEVANE

NOTES

Wilson's disease and Menkes' disease

The 7th International Symposium on Wilson's disease and Menkes' disease will be held in Vienna, Austria on 25–27 August 1995. Further information from: Prof Dr Peter Ferenci, Department of Internal Medicine IV, Gastroenterology and Hepatology, Währinger Gürtel 18–20, A-1090 Vienna, Austria. Tel: (43 1) 40 400 47 41; fax: (43 1) 40 400 47 350.

Neurogastroenterology

An International Symposium on Neurogastroenterology will be held on 10–11 November 1995 in Rome, Italy. Further information from: Dr Enrico Corazzari, Cattedra di Gastroenterologia I, Clinica

Medica II, Policlinico Umberto I, V.le del Policlinico, 00161, Rome, Italy. Tel/fax: 39 6-4469965.

Paediatric gastroenterology

The 1st International Congress of Pediatric Gastroenterology will be held in Jaipur, India on 12–16 December 1995. Further information from: Dr Balvir S Tomar, Head, Department of Pediatric Gastroenterology, 4 Govind Marg, Jaipur, 302 004, India. Tel: 91 141 604040 or 605050; fax: 91 141 563788.

Gastroenterology

A Postgraduate Gastroenterology Course will be held in Oxford on 7–10 January 1996. Further information from: Dr D P Jewell, Gastroenterology Unit, Radcliffe Infirmary, Woodstock Road, Oxford OX2 6HE. Tel: 01865 224829; fax: 01865 790792.

Inflammatory bowel disease

The International Inflammatory Bowel Disease Symposium will be held in Chester on 14–16 April 1996. Further information from: Prof Jonathan M Rhodes, Department of Medicine, Liverpool University, L69 3BX. Tel: 0151 706 3558; fax: 0151 706 5802.

ABIM announcement regarding change in training requirements for certification in gastroenterology

The American Board of Internal Medicine announces a new policy requiring three years of accredited training in a gastroenterology fellowship programme.

This decision follows a lengthy review by the ABIM Subspecialty Board on Gastroenterology and has the support of the American Gastroenterological Association, the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, the American Association for the Study of Liver Diseases, and the Gastroenterology Training Program Directors.

This new policy becomes effective for fellows entering gastroenterology fellowship training programmes in June 1996 and thereafter. Trainees who have questions about this policy should contact the American Board of Internal Medicine, 3624 Market Street, Philadelphia, Pennsylvania, 19104-2675, USA.

Falk Symposia

Details of Falk Symposia for 1995 and 1996 and the Basel Liver Week 1995 are now available. Further information from: Falk Foundation V, Leinenweberstraße 5, Postfach 65 29, D-79041 Freiburg, Germany. Fax: 0761/13034-59.

Sir Francis Avery Jones BSG Research Award 1996

Applications are invited by the Education

Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 1996 Award. Applications (**eighteen copies**) should include:

(1) A manuscript (2 A4 pages *only*) describing the work conducted.

(2) A bibliography of relevant personal publications.

(3) An outline of the proposed content of the lecture, including title.

(4) A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

Entrants must be 40 years or less on 31 December 1996 but need not be a member of the BSG. The recipient will be required to deliver a 40 minute lecture at the Spring meeting of the Society in 1996. Applications (**eighteen copies**) should be made to: The Honorary Secretary, BSG, 3 St Andrews Place, London NW1 4LB by 1 December 1995.

CORRECTIONS

The authors (Van't Hof *et al* 1995; **36**: 691–5) omitted an acknowledgement from their paper and would like to gratefully acknowledge the support of the Medical Research Council, South Africa.

An authors' error occurred in the paper by Khulusi *et al* (*Gut* 1995; **36**: 193–7). The second sentence under Clinical Methods should read 'One duodenal biopsy was obtained from the ulcer margin and two from the anterior duodenum', and on the same point the second paragraph of the Discussion should re-affirm that the three duodenal bulb biopsy specimens included 'two from the anterior wall'.

Some editorial errors occurred in the paper by Mothes *et al* (*Gut* 1995; **36**: 548–52). The tenth line of the Methods section should read 'was stopped by the addition of 10 ml acetic acid' and not 100 ml. In the legend to Fig 1: lane 2 should read 'gliadin (gli)' and not 'purified gliadin', lane 3 should read 'tryptic digested gliadin (t-gli)' and not 'gliadin'. The abscissa to Fig 3 should begin with zero and not 1. The legend to Fig 4 should read 'MHC expression by HT-29 cells – influence of gliadin (gli) (●), tryptic digested gliadin (t-gli) (○), casein (▼), tryptic digested casein (▽), and β lactoglobulin (■). Culture in the presence of interferon γ without addition of food derived peptides was 100%. Means of three or four (t-gli, four to seven) individual cultures are shown (*only two cultures performed). For sake of clarity the SEM is given in only one direction'.

Also, 'trypsin' and 'tryptic digestion' has been printed as 'tryptin' and tryptin digestion' throughout the text.