CLINICAL
SURGERY
INTERNATIONAL

1

LARGE BOWEL CANCER

EDITED BY
JEROME J. DECOSSE

CHURCHILL LIVINGSTONE

CLINICAL SURGERY INTERNATIONAL

VOL 1

Large Bowel Cancer

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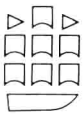

CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1981

CHURCHILL LIVINGSTONE
Medical Division of Longman Group Limited

Distributed in the United States of America by
Churchill Livingstone Inc., 19 West 44th Street, New York,
N.Y. 10036, and by associated companies,
branches and representatives throughout
the world.

First published 1981

ISBN 0 443 02126 0

British Library Cataloguing in Publication Data
Large bowel cancer—(Clinical surgery
International; Vol. 1)
1. Intestines—Cancer
I. DeCosse, Jerome J II. Series
616.9'94'34 RD668 80-49724

Printed and bound in Great Britain by
William Clowes (Beccles) Limited, Beccles and London

Large Bowel Cancer

CLINICAL SURGERY INTERNATIONAL

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Preface

With this first volume of Clinical Surgery International, a new series is launched. Each volume will emphasize one subject area and be scientifically sound. The subject areas will be timely and important to the practising surgeon.

We think the current volume on Large Bowel Cancer meets these criteria well. The authors have superbly developed their respective areas of expertise. If you have previously thought that the prevention and treatment of large bowel cancer is a static area without progress, we hope you will change your mind.

The epidemiology of large bowel cancer, an area of active worldwide investigation, is cleverly described by Stemmerman et al from Hawaii. Knowledge of inheritance of large bowel cancer is being extended from the classical polyposis syndromes to a better understanding of the more common high risk large bowel cancer families and this important topic is developed by Utsunomiya and his colleagues from Japan.

In contrast to the prominent view of a decade ago, the prevailing evidence today supports large bowel adenomas as precursors of large bowel cancer in the majority of patients and this evidence is developed by Morson and Day from the U.K. These findings have particular importance in preventive screening with hemoccult testing, as thoughtfully described by Winawer from the U.S.A.

The success of operative intervention in large bowel cancer depends in great part on the prevention of sepsis and on an appropriate operation. The role of intraluminal and systemic antibiotics is updated in a timely chapter by Condon and the appropriate extent of resection is described by Enker, both from the U.S.A.

The operative treatment of rectal cancer has been undergoing substantial change which has improved the likelihood of preservation of an intact gut. These improvements have resulted from lower anterior resections with conventional technique, the increasing popularity of stapling devices as developed in a chapter by Rothenberger et al, from the U.S.A., and the introduction of colo-anal anastomoses as described by Parks and Nicholls from the U.K. Another option, developed by Stearns from New York, is that of primary curative local treatment of selected patients with rectal cancer. In addition, some obstructing colon cancers lend themselves to resection and primary anastomosis and this subject is developed

by Fielding from London. The results of treatment are summerized authoritatively by John Goligher from Leeds.

The primary treatment of large bowel cancer increasingly requires multidisciplinary care. In separate chapters adjuvant radiation therapy is developed by Duncan from Scotland, chemotherapy by Taylor from England, and immunotherapy by Gill from Australia. Many options are available for effective management of patients with recurrent large bowel cancer and this subject is developed by Hughes et al from Australia.

Hence an experienced worldwide authorship have brought their particular expertise to this worldwide problem. We believe this volume is important to all who are involved in the management of patients with large bowel cancer.

1981 J.J.D.

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1 *Clues (true or false) to the origin of colorectal cancer*

G.N. STEMMERMANN, A.M.Y. NOMURA,
H. MOWER, G. GLOBER

Introduction

Carcinoma of the large bowel is not uniformly distributed among all populations. It is uncommon in Southern Asia and Equatorial Africa (Waterhouse et al, 1976), moderately common in Middle Europe; and very common in Northwestern Europe, the United States, Canada, and New Zealand (Table 1.1). Other diseases have similar international distributions. These include breast (Howell, 1976) and prostate carcinoma (Stemmermann, 1970), adenomatous and hyperplastic polyps of the colon, diverticulosis of the colon (Stemmermann & Yatani, 1973; Satoh et al, 1976), coronary heart disease (Robertson et al, 1977) and atherosclerosis (Stemmermann et al, 1976). Regional differences in the frequency of colorectal cancer are apparent in the United States, a high risk country. Blot's study (1976) of 3056 counties of the United States indicates that the tumour predominates in the north-east and is consistently elevated in counties with large populations, high income and high educational levels.

The similarity in the distribution of colorectal cancer and its companions forms the basis for the assumption that they arise from similar environmental events. This concept is reinforced by the experience of migrants who move from low risk countries to countries with a high risk for colorectal cancer. After acculturation they acquire the risk of the host country not only for bowel carcinoma, but also for its common companions. Berg & Howell (1974) have suggested that whereas a lot of rectal cancer is caused by the same factors that cause colon cancer, there is a second set of rectal cancers of different aetiology. This hypothesis is consistent with differences in location of rectal cancer in populations at low and high risk. Rectal cancer in high risk countries tend to be located in the upper rectum.

Several interdependent dietary hypotheses have been generated to account for the origin of large bowel carcinoma. These have been summarized by Burkitt (1975). After almost 10 years of vigorous international study, the high promise of many of these hypotheses remains unfulfilled. This chapter will document the hard data which identify high and low risk populations, cite both supportive and non-supportive evidence of relevant hypotheses and apply Burkitt's summary as a framework for discussion. Diseases that have little impact upon national or

international incidence rates for colorectal cancer (e.g. ulcerative colitis, familial polyposis) will not be discussed, although these are clearly associated with an increased risk for cancer.

Hypotheses

Large bowel cancer is related to factors characteristic of Western society

This premise would appear to be true if economic prosperity is a characteristic of Western society. The incidence and mortality rates of colorectal cancer in representative countries are summarized in Table 1.1. Migrants from countries at low risk for this tumour quickly acquire a high risk when they move to high risk countries. This has been observed among Japanese migrants to Hawaii (Haenszel et al, 1973) and among Polish migrants to the United States and to Australia (Staszewski et al, 1971). Chinese migrants to Hawaii come from South China where cancer of the large bowel is uncommon (Crowther et al, 1976). In Hawaii they experience rates of colorectal cancer that are among the highest in the world (Table 1.1). Under these circumstances the risk of colorectal cancer can be correlated with the socioeconomic level achieved by the non-Western group. In

Table 1.1[a] Incidence[b] (male) of colorectal cancer in different countries

	Colon	Rectum	Colorectal
Nigeria	1.3	1.2	2.5
Bay Area (USA)			
White	28.3	15.2	43.5
Black	24.0	10.8	34.8
Chinese	23.5	19.5	42.5
New Mexico (USA)			
White	23.3	12.1	35.4
American Indian	1.7	4.9	6.6
Connecticut (USA)	30.1	18.2	48.3
Birmingham (UK)	16.5	16.1	32.6
Denmark	16.2	16.7	32.9
Warsaw (Poland)	10.9	7.7	18.6
Miyagi (Japan)	5.6	6.8	12.4
Singapore			
Chinese	11.9	10.0	21.9
Malay	3.4	4.7	8.1
Canada (British Columbia)	24.1	10.5	34.5
New Zealand			
Maori	7.4	4.6	12.0
Non-Maori	23.0	15.4	38.4
Hawaii			
Japanese	22.4	16.3	38.7
Chinese	28.7	20.4	49.1
Caucasian	23.9	13.5	37.4
Hawaiian	14.1	9.4	23.5
Filipino	16.8	14.5	31.3

[a] Adapted from Waterhouse et al, 1976.
[b] Per 100 000, age-adjusted to world population.

Hawaii the rank order of family incomes among the dominant racial groups in 1977 (Annual Report, Statistics Department, Hawaii State Department of Health) is roughly the same as that for the incidence of colorectal cancer: Chinese $21 183; Japanese $19 431; Caucasian $19 005; Hawaiians $13 615; and Filipino $12 683. A similar association between income and colorectal cancer risk has also been recorded in Hong Kong (Crowther et al, 1976) and in Omaha-Douglas County, Nebraska (Lynch et al, 1975).

Conditions that favour the development of colorectal carcinoma favour the development of some non-neoplastic diseases (diverticulosis, hiatus hernia, varicose veins, myocardial infarction)

A high rate of diverticulosis of the colon is one of the most sensitive indications that a population has assumed a Western life style. This conclusion is based on autopsy observation among the Japanese in Hawaii and Japan (Table 1.2). Studies of Jewish migrants to Israel also indicate that diverticulosis is found more commonly in European than Asian Jews (Levy et al, 1977). Although a sensitive indicator of Westernization (Stemmermann & Yatani, 1973; Satoh et al, 1976) diverticulosis is not significantly related to colorectal cancer or to one of its known precursors – the adenomatous polyp (Stemmermann & Yatani, 1973; Eide & Stalsberg, 1979). A study of diverticulosis in Edinburgh (Eastwood, 1977) showed a significant negative association with persons who owned their own houses. Home ownership is an indicator of higher socioeconomic status, so that, in this respect, diverticulosis differs sharply from colorectal cancer.

Evidence that fibre depletion routinely increases luminal pressure, augments bowel wall tension and eventually causes emergence of diverticula is not satisfactory (Mendeloff, 1978), but there is evidence that bran supplements are effective in the treatment of painful diverticulitis.

The numerous races of Hawaii experience different risks for other diseases (Glober & Stemmermann, 1980). These differences show no internal consistency (Table 1.3) and none appears to correlate well with colorectal cancer rates in these races (Table 1.1).

Table 1.2 Comparison of Japanese living in Hawaii and Japan

	No. of patients	No. of adenomatous polyps (%)	No. of hyperplastic polyps (%)	No. of diverticula (%)
Hawaii[a]				
Males	125	80 (64)	99 (79)	67 (54)
Females	77	45 (58)	55 (71)	38 (49)
Total	202	125 (62)	154 (76)	105 (52)
Japan[b]				
Males	376	129 (34)	9 (2)	1 (0.3)
Females	293	50 (17)	9 (3)	5 (1.7)
Total	669	179 (27)	18 (3)	6 (0.9)

[a] Data are from Stemmermann and Yatani (1973).
[b] Data are from Satoh et al (1976).

Table 1.3 Disease rates[a] in hospital inpatients in Hawaii, sex and ethnic groups, January 1974—July 1978

Disease		Caucasian	Japanese	Chinese	Filipino	Hawaiian
Diverticulosis	male	810	529	468	321	297
	female	821	425	478	320	366
Hiatus hernia	male	523	73	137	115	81
	female	535	51	162	158	138
Oesophagitis	male	289	94	91	94	110
	female	264	67	169	187	82
Cholecystitis	male	531	541	915	538	297
	female	960	933	1637	1489	1382
Appendicitis	male	209	267	202	350	331
	female	219	206	201	395	249
Varicose veins	male	57	8	11	25	96
	female	41	5	17	0	73
Haemorrhoids	male	79	92	178	136	118
	female	67	63	121	80	109

[a] Rate per 100 000 (age 15—75+—age standardized to world population).

It has been observed that countries with high rates of colorectal cancer also have high rates of coronary heart disease (CHD). Finland, with high CHD rates (Segi et al, 1966) and low colorectal cancer rates (Waterhouse et al, 1976), is an exception to this pattern. The annual U.S. State Department of Health Stastical Report noted that in Hawaii, the 1950 age-adjusted mortality rates per 100 000 for CHD in males were: Caucasians, 280; Japanese, 78; Chinese, 142; Filipinos, 80; and Hawaiians and part-Hawaiians, 320.

By 1970, the mortality rate for coronary heart disease (per 100 000) had risen to 236 among the Filipinos as opposed to only 160 for the Japanese, 194 for the Chinese, 360 among the Caucasians, and 380 among the Hawaiians. During these 20 years the Filipinos experienced a rapid increase in social and economic status and many had moved from rural areas to the more densely populated regions of metropolitan Hawaii (Hackenberg et al, 1978). In other words, the Hawaiians with the highest CHD mortality rates and Filipinos with the most rapid rise in CHD rates have a low risk of colorectal cancer; whereas the Chinese, with a low CHD risk, have the highest incidence of colorectal carcinoma.

The serum cholesterol level in patients who died from CHD and from colorectal cancer in the longitudinal Japan – Hawaii Cancer Study of Hawaii Japanese men was not the same (Table 1.4). As might be expected the mean cholesterol level was significantly higher in men who died of CHD than among the control population, but those who subsequently died of colon cancer had lower blood cholesterols than the controls. These findings are similar to those of Rose et al, (1974).

Conditions that favour the development of colorectal cancer favour the development of other neoplastic diseases

It is now clear that trends and international distributions of several cancers are similar. Tumours that have been linked to Western social patterns are cancer of the ovary, endometrium, breast, prostate and large bowel. Breast cancer and colorectal cancer show particularly close associations (Howell, 1976). Fraumeni et

Table 1.4[a] Standardized logistic coefficients for the regression of specified causes of death (in 9 years) on serum cholesterol. The Honolulu Heart Study

Cause	Bivariate	Multivariate[b]
Cancer (all sites)	−0.402‡	−0.342‡
Oesophageal cancer	−1.10†	−0.822*
Stomach cancer	−0.329	−0.200
Colon cancer	−0.831†	−0.867‡
Liver cancer	−0.714*	−0.750*
Lung cancer	−0.544†	−0.474*
Other cancer	−0.398†	−0.375*
CHD	0.384‡	0.332‡
Diabetes	0.924‡	0.880‡

* Coefficient differs significantly from zero ($P < 0.05$)
† Coefficient differs significantly from zero ($P < 0.01$)
‡ Coefficient differs significantly from zero ($P < 0.001$)
[a] Data from Kagan et al 1980 (submitted for publication).
[b] Age, serum cholesterol, SBP, cigarettes/day, alcohol, relative weight.

al (1969), in a study of neoplastic disease in unmarried women, noted an excess of large bowel cancer, especially in post-menopausal women, with high frequencies of breast, endometrial and ovarian tumours as well. A basis for an association of large bowel cancer with mammary cancer has not been established. Hawaiians and Maoris constitute an exception to this basic pattern, with high rates of endometrial and breast cancer, but low rates of bowel cancer (Waterhouse et al, 1976). This discrepancy suggests that the association of these tumours is due either to the influence of synchronous but independent causes, or to a genetically controlled factor in Polynesians that lessens the risk of cancer induction in the bowel but not in the breast.

Adenomatous polyps of the large bowel are benign epithelial neoplasms that are closely associated with invasive colorectal carcinoma. They are common in populations at high risk for bowel cancer (Bremner & Ackerman, 1970; Correa et al, 1972; Stemmermann & Yatani, 1973; Satoh et al, 1976). Most pathologists agree that many large bowel cancers arise in adenomatous polyps (Morson & Bussey, 1970). Japanese migrants who experience an increased risk of colorectal cancer also experience an increased risk of adenoma, (Table 1.2). Scandinavian (Eide & Stalsberg, 1978) and Hawaii studies (Stemmermann & Yatani, 1973) have suggested that adenomas and carcinomas favour different segments of the bowel, adenomas being more common in the ascending colon, and carcinomas more common in the sigmoid colon. It is possible that the rapidity of the adenoma to carcinoma sequence is dose-dependent and that high concentrations of carcinogens in the sigmoid colon result in rapid effacement of the adenoma.

The hyperplastic polyp of the colon and rectum, like adenoma and diverticulosis, increases in frequency among migrants to high risk societies (Table 1.2). Although it is a non-neoplastic tissue change (Morson & Bussey, 1970) hyperplastic polyps are most common at those sites which are most vulnerable to cancer. *Is this lesion a precursor of cancer?* This is a matter of some controversy. There are very few adenomas that do not contain some hyperplastic glands, but this could be explained on the basis of distortions of cell migration secondary to the

adenomatous process. Hayashi et al,(1974) have suggested that the process is the result of slowed crypt to surface migration and delayed exfoliation; and the surface cells have the ultrastructural appearance of hypermaturity rather than hyperplasia. If functional hypermaturity accompanies morphologic hypermaturity, the epithelium of these mucosal excrescences might increase the absorbtive efficiency of the affected bowel for water so as to increase the dose of carcinogen in the affected bowel lumen and thereby increase the concentration of carcinogen at the level of the cell surface. This could explain the close site association with carcinoma and the high frequency of hyperplastic polyps in populations at high risk for the tumour.

Persons at high risk for large bowel cancer have slow bowel transit times (BTT) and produce small firm stools.

This observation was based on comparisons of the BTT in small numbers of unselected African Blacks (a low risk population) with equally small numbers of British subjects (a high risk population), unmatched by age and sex (Burkitt et al, 1972). Comparative studies with larger numbers of age- and sex-matched Hawaii and indigenous Japanese and of Hawaii Caucasians (Glober et al, 1977), however, showed no association of BTT with the risk of either colorectal cancer or its common companions (Table 1.5). The BTT of Hawaii Japanese was similar to that of indigenous Japanese in spite of a threefold postmigration increase in the frequency of large bowel cancer. The BTT of Hawaii Caucasians was similar to the reported BTT in British subjects and much longer than that of Hawaii Japanese in spite of a similar incidence of colorectal cancer in both Hawaii races. This same study, however, did support the premise that the stool weight was heavier in the low risk indigenous Japanese population. Jensen & MacLennan (1979) also failed to confirm an association between bowel cancer risk and BTT in their studies of Finnish and Danish subjects.

The diet of Western societies favours the development of a colonic microflora capable of generating carcinogens or co-carcinogens from bile acids (Hill & Aries, 1971)

A refinement of this hypothesis suggests that *Clostridium paraputrificum* fills this role (Hill, 1974). Studies have been undertaken to compare the faecal flora of high and low risk populations. These have included comparisons between: high risk Danes and low risk Finns (MacLennan, 1977); Seventh Day Adventists with non-

Table 1.5 Mean bowel transit times and stool weight by race and country

	Hawaii		
	Caucasian (HC)	Japanese (HJ)	Japanese (JJ) (Akita Pref.)
Bowel transit times (h)	56.2[a] (25)[b]	31.4[a] (67)	33.9[a] (28)
Stool weight (g)	119.7[c] (18)	120.7[c] (47)	194.7[c] (17)

[a] HC vs. JJ, P 0.001; HC vs. JJ, P 0.005; HJ vs. JJ, $P = 0.47$ (by two-tailed t-test).
[b] Number of subjects.
[c] HC vs. HJ, P 0.50; HC vs. JJ, P 0.01; HJ vs. JJ, $P < 0.001$.

vegetarian controls (Feingold et al, 1977; Goldberg et al, 1977); Japanese–Americans on Western and traditional Japanese diets (Feingold, 1974); Hong Kong Chinese at different levels of income (Crowther et al, 1976); students on meat-free and high beef diets (Maier et al, 1974) elemental diets (Bounous & Devroede, 1974); diets with different amounts of fat (Cummings et al, 1978); patients with large bowel cancer and non-hereditary large bowel polyps (Mastromarino et al, 1978). Certain organisms have been identified in high risk populations but the results of these studies have not been consistent and none has succeeded in linking *C. paraputrificum* with colorectal carcinoma. A major problem of many of these studies is the small number of persons studied. It is unlikely that bacteriologic surveys of high and low risk populations will identify an organism specifically related to colorectal carcinogenesis. Moore & Haldeman (1974) note that the colonic microflora of each person are very complex and also that variations within populations are very great. Bacteria comprise 40 per cent of the faecal mass and these authors have isolated 100 distinct types of bacteria from each risk group, half of which had not been previously described. One person may have up to 400 species of bacteria in the gut. They point out, however, that low risk populations tend to maintain higher concentrations of a few species, whereas high risk groups usually have a more heterogenous flora. These findings do not exclude a bacterial role in carcinogenesis, but do suggest that a bacteriologic screen is not likely to discover it.

Persons consuming large amounts of fat are at high risk for developing colorectal carcinoma

Support for this concept derives from observations that the diets of Westernised populations have a larger proportion of fat, particularly animal fat, than do those of low risk populations (Wynder & Reddy, 1974); and a high fat intake has been implied from case control studies that have shown a positive association between colorectal cancer and beef intake (Haenszel et al, 1973).

If CHD and colorectal cancer each stem from excess dietary fat one might expect an association to be confirmed in prospective studies. A comparison of diets in Hiroshima, Japan (low risk for CHD and colorectal cancer) and Honolulu Japanese (high risk for CHD and colorectal cancer) does show a much higher annual fat consumption in Hawaii (Kagan et al, 1974), but equally striking differences are also noted in the amounts of protein and refined carbohydrates (Table 1.6).

Table 1.6 Mean diet values, 24 h recall

Nutrient	Japanese	Hawaii Japanese
Calories	2132	2274
Total protein (g)	76	94
Animal protein	40	71
Vegetable protein	37	24
Total fat (g)	36	85
Total carbohydrate (g)	339	260
Alcohol (g)	28	13
Cholesterol (mg)	457	545