Colo-Rectal Cancer

A series of Workshops on the Biology of Human Cancer
Report No. 2

Edited by J.H. Weisburger, Bandaru S. Reddy and David L. Joftes

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COLO-RECTAL CANCER

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WORKSHOP ON COLO-RECTAL CANCER

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<u>INTRODUCTION</u>

This report reviews the current status of factors bearing on cancer of the large bowel. Particular emphasis is given to the aetiology and pathogenesis of the disease, to animal models, to the early diagnosis and immunology and, finally to therapy, including immunological approaches thereto.

Epidemiologic data provide background information on elements associated with colo-rectal cancer risk, and suggest that major causative elements are associated with diet and, in particular, high fat diets. This is documented not only in human studies, but also in parallel animal observations. Reliable animal models, developed over the last 20 years, are of considerable value in studying mechanisms under highly controlled conditions.

It is also suggested that cancer of the rectum may originate from factors not identical with colonic cancer, for rectal cancer does not vary as much in incidence between high and low risk regions, and also exhibits a more pronounced sex-linked effect, with a male/female ratio of 1.4 for rectal cancer and near unity for colon cancer. Furthermore, cancer of the rectum exhibits a decreasing trend in the United States whereas cancer of the colon has shown constant or even slightly increased incidence over the last 25 years.

Recent discoveries on foetal antigens which initially appeared specific for colo-rectal cancer, but which now are found in a

variety of neoplastic and non-neoplastic diseases, have aroused
new interest and activity in the development of improved means
of early diagnosis of colo-rectal cancer. These efforts have
also led to better understanding of certain aspects of pathogenesis,
the development of cell culture systems of neoplastic but not
yet of non-neoplastic colon, and also provided wider horizons in the
immunology and immunotherapy of colo-rectal cancer. A great deal
of work remains to be done to complement the traditional ways
of management of existing colo-rectal disease, through surgery
and radiotherapy, by newer approaches of chemotherapy based on
rational developments obtained through the study of cell kinetics
and cell turnover. More insight into diseases predisposing to
colo-rectal cancer such as familial polyposis and ulcerative
colitis may also provide discriminant leads to the role played
by genetic and environmental components which ultimately control
the varied steps leading to colo-rectal cancer. Thus, exogenous
factors in the environment such as diet interact with endogenous
elements such as metabolic capability, in part a function of genetics,
in determining the risk of an individual.

It is these interrelationships, which when considered by a
multidisciplinary experimental and clinical approach, provide the
most likely leads towards an understanding of the mechanisms of
disease causation and prevention, of means of earlier diagnosis
and, therefore, more successful management, and of improved
rational modalities of treatment.

A panel of recognized international experts have provided
an overview of the current status of the varied aspects of colo-

rectal cancer. It is hoped that this document will be an instrument
providing: (*i*) The research community with a concise statement
of current activities, (*ii*) The practicing physician with an
understanding of advances which will facilitate his management of
patients, and finally, (*iii*) Program planners with the necessary
background information.

In the light of the current status, future efforts can be
fostered on an international scale to further improve our know-
ledge of colo-rectal cancer and to provide a basis for the ultimate
success in disease control, namely disease prevention for future
generations, and successful eradication for the current generation.
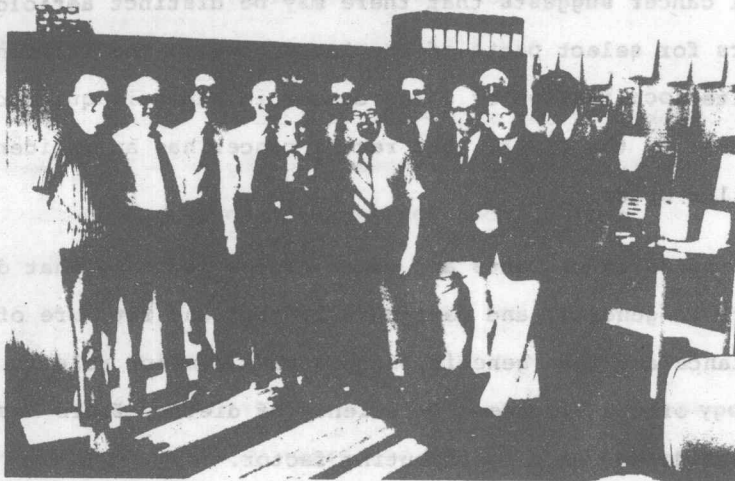
Workshop participants at UICC Headquarters. From left to right :
Dr. H. Sjögren, Dr. P. Magee, Dr. L. M. Franks, Dr. M. Lipkin, Dr. M. Hill,
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SUMMARY

The incidence of colo-rectal cancer is generally high in
populations with a Western European culture and is generally
low in Africa, Asia and South America; it is highest in the
United States, New Zealand and Scotland. In the U.S.A. 5% of
the people can be expected to develop colo-rectal cancer; in the
U.S. colon and rectum cancer has a higher incidence than any
other cancer except skin cancer. Colon cancer is, but rectal
cancer is not increasing. The sub-site distribution of colo-
rectal cancer suggests that there may be distinct aetiologic
factors for select parts of the large bowel. The incidence and
sub-site localisation of colon cancer in Japan is quite different
from that in the U.S.A., but rectal cancer has an incidence of
a similar order.

Studies of migrants and other groups indicate that dietary
factors in general, and particularly meat and fat, are of major
importance and that genetic factors play a minor role in the
aetiology of the disease. Deficiency of dietary fibre has not
been validated as a contributing factor.

Most experimental studies have supported the role of dietary
fat.

One suggested mechanism accounting for the role of fat in

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colo-rectal cancer involves the production of carcinogens and/or
co-carcinogens from bile acids or other endogenous metabolites
by the gut bacteria. This is compatible with the results of
studies comparing populations with high, low or intermediate
incidences of the disease, and of case control studies. The
level of dietary fat influences both the amount and type of bile
acid and probably the intestinal flora acting on it.

Description of the distribution of colo-rectal cancer in terms of age, sex, ethnic group, geography etc. (descriptive epidemiology) has provided clues to aetiology. Many disciplines are involved in studying the determinants of disease frequency in man. Traditionally epidemiology has drawn on clinical medicine, pathology and biostatistics to explain disease frequency (analytic epidemiology). Studies in association with other disciplines, including nutrition, biochemistry, enzymology, microbiology, organic chemistry and chemical carcinogenesis may be termed metabolic epidemiology.

A. DESCRIPTIVE EPIDEMIOLOGY OF COLO-RECTAL CANCER

Clues to aetiology of colo-rectal cancer have been derived mainly from studies of its geographic distribution and of migrants. Other aspects such as the sub-site distribution and the identification of high risk groups have also contributed. The study of variation by age, sex and time has so far been less rewarding.

1. *Geography and demography*

The main features of the geographic and ethnic distribution of the cancer of the colon and rectum are illustrated in table 1 (UICC, 1970). The highest incidence rates are found mainly in Western Europe and the Anglo-Saxon world. Intermediate rates are found, for example, in Eastern Europe, while the lowest incidence is found in Africa, Asia and Latin America. Although most of Latin America has a very low incidence (e.g. Cali, Colombia), mortality rates in Uruguay and Argentina are similar to those found in Western Europe and the U.S.A. In Israel,

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colo-rectal cancer incidence in Jews from Asia and North Africa is half that in Jews from Eastern Europe, an area with intermediate incidence. Although much more knowledge is needed on frequency by region and groups within different countries, the international distribution of colo-rectal cancer suggests that high rates are confined to populations with Western European cultural traditions, and are not related to industrialisation (e.g. Japan, table 1).

Although some of the geographic and ethnic differences may be due to the well-known artifacts of inaccurate diagnosis and incomplete reporting, these can account for only a small proportion of the international variation. Further, in Scandinavia the methods of diagnosis in deaths reported as colon cancer were similar in Denmark and Finland (Jensen et al., 1974) and thus the differences (table 1) appear to be valid.

Urban populations generally have higher risks for colo-rectal cancer, e.g. in Poland (table 1). In the United States the incidence of colon cancer (but not rectal) doubled in the Black population between 1947 and 1969 (Third National Cancer Survey, 1971; Cutler, 1975). This followed the internal migration of Blacks from rural areas to cities. Although socio-economic differences in risk have not been prominent in Western Europe and the U.S.A., recent studies in populations with low risk (Cali-Colombia and Hong Kong) have shown a 2-fold higher risk in persons of high socio-economic status.

2. *Migrants*

Evidence of the importance of environmental rather than

genetic factors in determining the geographic differences in colo-rectal cancer incidence is provided by studies of migrants to the U.S.A. and Australia. Although migrants are not a representative sample of their native populations, they are probably genetically more similar to it than to their new host population. However, their cultural and culinary practices change gradually after migration (Steiner, 1954).

Among migrants to the U.S.A., the Japanese (Buell and Dunn, 1965), Polish (Staszewski and Haenszel, 1965), and Norwegian (Bjelke, 1974) have been the most extensively studied. American Japanese comprise both Japanese-born (Issei) and U.S.-born (Nisei). Both groups have a higher incidence of colo-rectal cancer than comparable populations in Japan, but the differences are greater in males than in females (table 1). The increased risk in the Issei indicates the importance of environmental factors during adult life in the aetiology of colo-rectal cancer.

The increased incidence in other American migrants is illustrated in table 1. Blacks in Alameda County, California have much greater incidence than Blacks from Ibadan, Nigeria (which represents the population of West Africa from which many American Blacks originated). Further support for an environmental dietary influence and living habits in the development of colo-rectal cancer derives from a study of Asian migrants in Kenya (Chopra et al., 1975). Such studies of migrant populations tell us nothing of detailed relationships, e.g. between diet and cancer; however, they give information on the relative contribution of genetic and environmental factors which have rapid and those which

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have delayed effects.

3. *Distribution of cancer by sub-site within the large bowel*

The anatomical localisation of tumours within the colon and rectum varies with overall incidence. Low risk populations such as those from Ibadan, Bombay and Miyagi have a 'greater proportion of tumours in the caecum and ascending colon, than do high risk populations such as those from Denmark, which have a concentration of tumours in the sigmoid colon (Haenszel and Correa, 1971; de Jong et al., 1971). A recent study has shown that cancers in the upper half of the rectum, i.e., those lying above 8 cm from the pectinate line are epidemiologically related to colon cancer (Berg and Howell, 1974).

Haenszel and Correa (1971) proposed a four stage epidemiologic model for colon cancer which is essentially: (*i*) In the "endemic" or low incidence situation, colon cancers are concentrated in the caecum and ascending colon. (*ii*) The appearance of new aetiologic factors in such populations results in an increased incidence in the sigmoid colon, first among older men and (*iii*) later among older women. (*iv*) The final phase is characteristically a rise in caecum and ascending colon cancer. A recent analysis by Cady et al. (1974) in Boston supports the final phase concept of Haenszel and Correa (1971). The implications of data on the sub-site distribution are that there may be more than one set of aetiological factors involved in colo-rectal cancer;

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the observed distribution of tumours within the large bowel may

thus depend on their relative proportions (see also Correa and

Haenszel, 1975).

More information is needed on the detailed sub-site distribu-

tion in the rectum of populations at varied risk. Due to different

and shifting definitions of the location of the recto-sigmoid

junction (Berg and Howell, 1974), such studies will probably

need to be based on prospective international data collected

under rules which ensure comparability.

4. *Familial occurrence*

Simple Mendelian disorders such as hereditary adenomatosis

of colon and rectum (familial polyposis) account for only a small

fraction of colo-rectal cancer cases. Familial occurrence without

a detectable Mendelian pattern is being increasingly recognised

(Fraumeni and Mulvihill, 1975). A study from London showed

approximately 5-fold increased risk in siblings of index cases

of cancer of the colon or rectum (Lovett, 1974). However, this

study did not report on the risk in spouses of index cases.

Similarity between the diet of adult siblings as well as between

spouses has been shown by Bjelke (1975) who found an increased

risk in a small number of spouses of colo-rectal cancer cases

compared with controls.

Investigation of colo-rectal cancer in families may contribute

to knowledge of aetiology in two ways: (*i*) they may facilitate

prospective studies by identifying persons at high risk who do

not yet have colo-rectal cancer and thus facilitating prospective
studies; (*ii*) by sorting out the relative roles of genetic and
environmental factors within a population.

5. *Prevalence and site distribution of polyps in the large bowel*

Among populations there is a broad association between
adenomatous polyps and colo-rectal cancer. Both are of
extremely low frequency in the South African Bantu (Bremner and
Ackerman, 1970). A comparison of a large autopsy series from
Cali, Colombia (low risk) with high risk countries suggested a
statistical association between colon cancer incidence and prevalence
of adenomas and with atypical cellular changes in adenomas
(Correa et al., 1972) thus supporting findings of earlier studies
in high risk countries alone.

However, the frequency distribution of adenomatous polyps
within the large bowel is different from that of carcinoma;
polyps are relatively less frequent in the rectum than carcinoma
in both sexes in populations with high and low colo-rectal cancer
risk (Correa et al., 1972). Colon carcinomas are concentrated
in the sigmoid of Hawaiian Japanese, whereas 44% of adenomatous
polyps are found in the caecum and ascending colon (Stemmerman
and Yatami, 1973). These differences in distribution suggest
that the probability of an adenoma becoming malignant varies by
site within the large bowel as well as by size and morphological
type (Morson, 1974). In a large Swedish registry of hereditary

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adenomatosis of the colon and rectum, a condition in which adenomas
are distributed in large numbers throughout the large bowel,
the sub-site distribution of 229 carcinomas within the colon and
rectum parallels colo-rectal cancer in the general population of
Sweden (Almy and Licznerski, 1973).

6. *Occupational exposure*

Selikoff et al. (1973) reported an excess of cancer of the
colon and rectum in U.S. asbestos insulation workers (26 cases
versus 17.51 expected). A similar excess has been found among
insulation workers in Belfast (Elmes and Simpson, 1971).

B. ANALYTIC EPIDEMIOLOGY

Studies attempting to explain the frequency of colo-rectal
cancer have used correlation and case-control studies.

1. *Correlation Analysis*

Geographic correlations between cancer frequency and national
or regional consumption of selected foods and beverages have been
used to select between possible hypotheses for testing by case-
control and cohort studies. Correlation between colo-rectal cancer
frequency and that of other cancers and diseases may provide
clues to common aetiological factors. Such analyses are based
on average exposure data from populations where individual
exposure may be heterogeneous. The resulting problems of inter-
pretation have been summarized by Breslow and Enstrom, (1974).

Based on Japanese data and case-control studies, Wynder