ADVANCES IN CANCER RESEARCH

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SIDNEY WEINHOUSE

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THE EPIDEMIOLOGY OF LARGE-BOWEL CANCER

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I. Introduction

Prior to the 1960 decade, large-bowel cancer received only cursory attention from epidemiologists. For many years virtually all the epidemiological data for this site had been assembled as a by-product of periodic multipurpose analyses of death certificates and of reports of newly diagnosed cancer cases sent to tumor registries. Within the digestive tract, stomach attracted more attention and the systematic assembly of descriptive data to develop or test etiological hypotheses for cancer of the colon and rectum remained a neglected field.

Why did this condition prevail? While there is no certain answer, one probable reason was that epidemiologists in North America and western Europe were bemused by the impression of little variation in risk for large-bowel cancer within their respective countries. This, coupled with the fact that clinical investigators had assembled substantial amounts of data on genetically determined diseases (familial polyposis, Gardner's syndrome, Crohn's disease, etc.) associated with high risks for large-bowel cancer that emphasized the role of host characteristics, tended to direct interest away from the study of possible environmental factors. The outcome was that epidemiologists in North America and western Europe ignored large bowel because they viewed the local experience as "normal," while investigators working in low-risk countries had little incentive to study these neoplasms, which were unimportant sources of morbidity in their populations.

The turning point in the epidemiology of large-bowel cancer came with the systematic compilation of incidence data from cancer registries throughout the world. While these efforts were antedated by Segi's compilations of cancer mortality statistics beginning with 1950 (Segi, 1960), which described sizable gradients in large-bowel cancer death rates—the differences being on the order of 6 to 1 between countries at the two extremes of the risk spectrum—the mortality data had been discounted on the grounds that the contrasts were inflated by intercountry differences in diagnostic and treatment facilities and death certification practices. This attitude began to change when the data in the first edition of "Cancer Incidence in Five Continents" (Doll *et al.*, 1966) proved to be consistent with and reinforced the

mortality findings. Within a short time span, the concept of substantial intercountry variation in large-bowel cancer risk gained wide acceptance as a prime epidemiologic characteristic of this disease. This feature was stressed at the meeting of the International Working Party of the World Organization of Gastroenterology in 1963, which also noted differences in the presentation of tumors by anatomical segment in high- and low-risk populations (Boyd *et al.*, 1964). Interpopulation differences were the source and inspiration for Burkitt's hypothesis on the causal role of a low-bulk, high-starch diet in large-bowel cancer (Burkitt, 1971a; Burkitt *et al.*, 1972). Burkitt's conjectures have been followed by more systematic correlations of global data on food consumption and incidence and/or mortality from large-bowel cancer (Howell, 1974, 1975; Armstrong and Doll, 1975), which have generated other dietary hypotheses.

The international comparisons pointing to environmental factors as important risk determinants have been reinforced by observations that showed migrants coming to the United States from low-risk European countries and Japan to acquire within their lifetime the high risks characteristic of the host population of U.S. whites (Haenszel, 1961; Haenszel and Kurihara, 1968). The latter in turn stimulated studies of diet and related factors among migrants and control populations in the countries of origin and destination (Haenszel *et al.*, 1973; Bjelke, 1974).

The contrasts of high- and low-risk populations revived some earlier work on associated pathologies. Helwig's autopsy studies in St. Louis on the distribution of adenomatous polyps, published in 1947, had described a congruence in the anatomical distribution of adenomatous polyps and intestinal carcinomas and identified adenomatous polyps as a possible precursor lesion (Helwig, 1947). Helwig's findings stimulated other work in the United States (Blatt, 1961; Chapman, 1963; Arminski and McLean, 1964; Spratt *et al.*, 1958), but the issue of presence or absence of congruence in the distribution of polyps and tumors remained unresolved, not because of lack of diligence or ingenuity on the part of the investigators, but primarily from the inability of observational settings within a single country to distinguish and choose among the alternatives. Correa *et al.* (1972) in their work stressed the need for comparative autopsy studies in populations at high risk and low risk to large-bowel cancer. This approach established striking differences in prevalence and anatomic distribution in the two types of populations and strengthened the case for intestinal polyps (or certain subtypes of polyps) as precursors of large-bowel carcinomas. The polyp findings raise the possibility of transforming the epidemiology

of large-bowel cancer into the epidemiology of intestinal polyps and other suspect antecedent conditions, a step that would facilitate investigations of dietary factors. Diet histories are notoriously difficult to collect and the problems of response are magnified when the data sought relate to practices in the distant past. Case-control studies that focus on a condition presenting early in the sequence of events culminating in large-bowel cancer should afford better opportunities of uncovering dietary associations.

Wynder and Shigematsu (1967) reviewed the literature up to 1966. Haenszel and Correa (1971) later considered the epidemiological findings on magnitude of incidence rates, the sex–age patterns of incidence, and the anatomic localization of tumors in relation to the findings from autopsy studies on the distribution of intestinal polyps. Undoubtedly the most comprehensive review of the epidemiological literature bearing on large-bowel cancer has been carried out by Bjelke as part of his studies of digestive tract cancers among Norwegian "sedentes" and migrants. Bjelke's complete dissertation (1973) is available only as a microfilm reproduction, but a summary of the dissertation highlights has been published (Bjelke, 1974). The present review touches on many of the topics covered in earlier reviews, and when possible the findings have been updated. We have made extensive reference to the most recent cancer registry data published in the third edition of "Cancer Incidence in Five Continents" (Waterhouse *et al.*, 1976) and have considered information from comparative studies of intestinal polyps in high- and low-risk populations that has become available since 1970. An assessment of animal studies and the development of animal models to test and elaborate mechanisms for the production of large-bowel tumors, which have been stimulated by the epidemiological findings, is outside the scope of this review. We do attempt to identify profitable areas for epidemiological studies that are suggested by findings from animal work, since a review of the rapidly expanding field presented by research on large-bowel cancer requires one to place past and current events in context of their implications for future work.

II. Demographic Factors

A. Intercountry Variation

"Cancer Incidence in Five Continents," third edition (Waterhouse *et al.*, 1976), is the primary source of information on interpopulation variation in risk of large-bowel cancer. Figure 1 summarizes the inci-

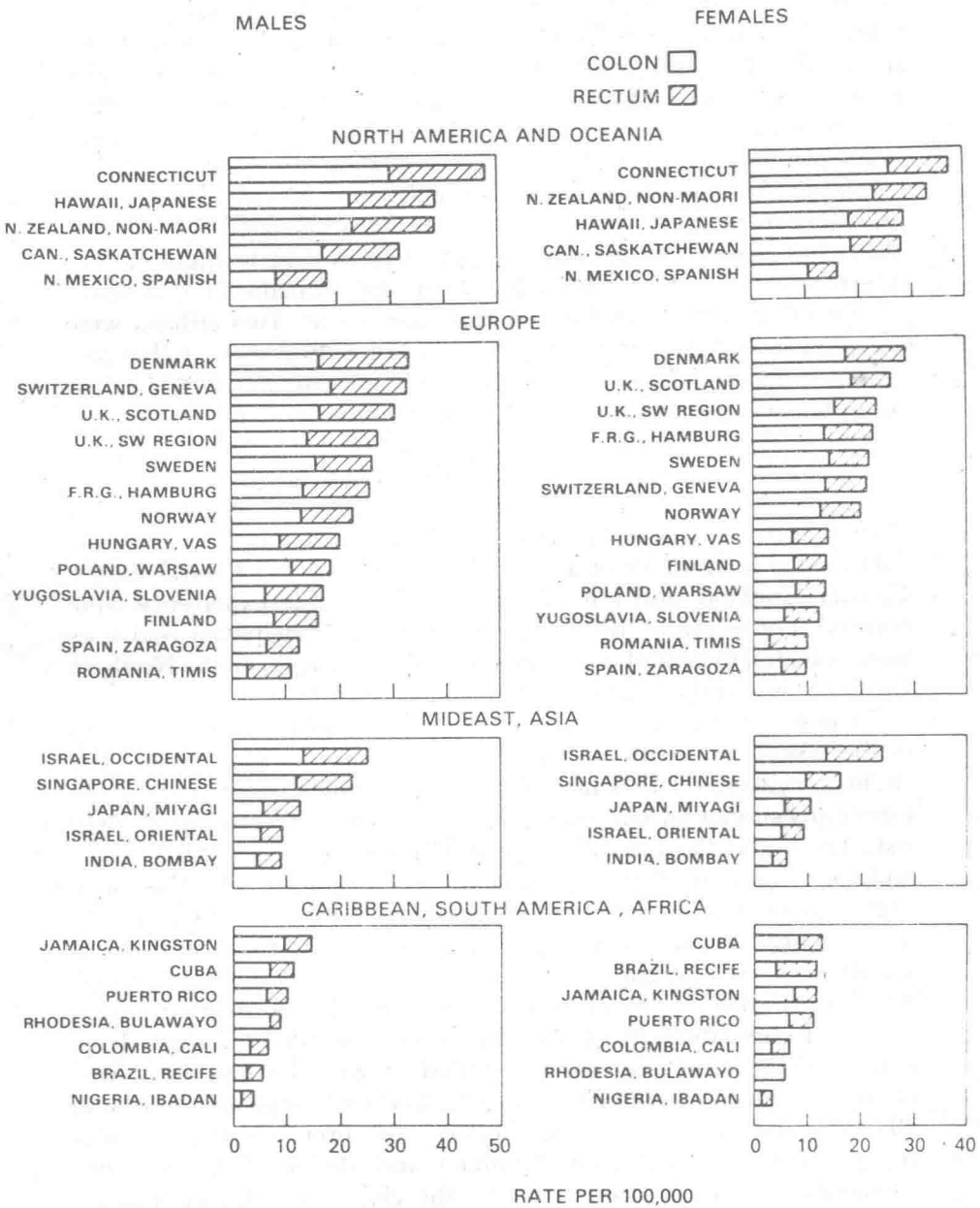

FIG. 1. Age-adjusted incidence rates for cancer of the large bowel (colon and rectum), by sex. Selected registries, variable periods close to 1970. Source: Waterhouse *et al.* (1976).

dence rates, age-adjusted to the world population standard, for selected registries contributing to that publication. The conventional subdivision of large bowel into colon and rectum is somewhat arbitrary and differences in classification and reporting practices may have introduced incomparabilities into the results for the two anatomical segments. For this reason the initial presentation represented by Fig. 1 emphasizes the incidence rates for total large bowel, although the separate contributions for colon and rectum are indicated. The presentation has been organized by regions of the world to highlight the interregional variation which has been and remains a distinctive epidemiological characteristic of this cancer site. Two criteria were followed for the inclusion of registries in Fig. 1. Registries with representative experience for each region were chosen, supplemented by countries deviating from regional norms to underscore the presence of variations in risks within individual regions. The inclusion of the Spanish-surname population of New Mexico (of predominantly Mexican origin) documents the presence within the United States of groups at relatively low risk to bowel cancer. To condense the presentation, data available from several cancer registries in the United States, Canada, England, and Japan reporting comparable experience were omitted. For example, the Connecticut and Saskatchewan registries were selected to describe the rates typical of registries in the Northern United States and Canada.

For males the ratios in risk between populations at the two extremes of the disease spectrum are on the order of 6–8 to 1; a similar, but slightly weaker, relationship prevails for females. Both sexes yield essentially similar rankings of countries by order of large-bowel cancer risk. The highest incidence is reported by registries in North America and Oceania (United States, Canada, New Zealand). The European registries assume an intermediate position and can be further subdivided into western Europe and Scandinavia and eastern Europe and the Balkans, the first group of countries having generally higher rates. The lowest rates are found in Asia, Africa, and Latin America.

Not all populations are covered by cancer registries, and we have consulted the mortality data assembled by Segi for countries with adequate diagnostic and medical care facilities (Segi and Kurihara, 1972) and the relative frequency information from hospital and necropsy sources compiled by Dunham and Bailar (1968) for supplementary information to round out the global description of large-bowel cancer risk. The essential findings of Dunham and Bailar on the geographical distribution of large-bowel cancer are contained in the map for males reproduced from their publication (Fig. 2). Their infor-

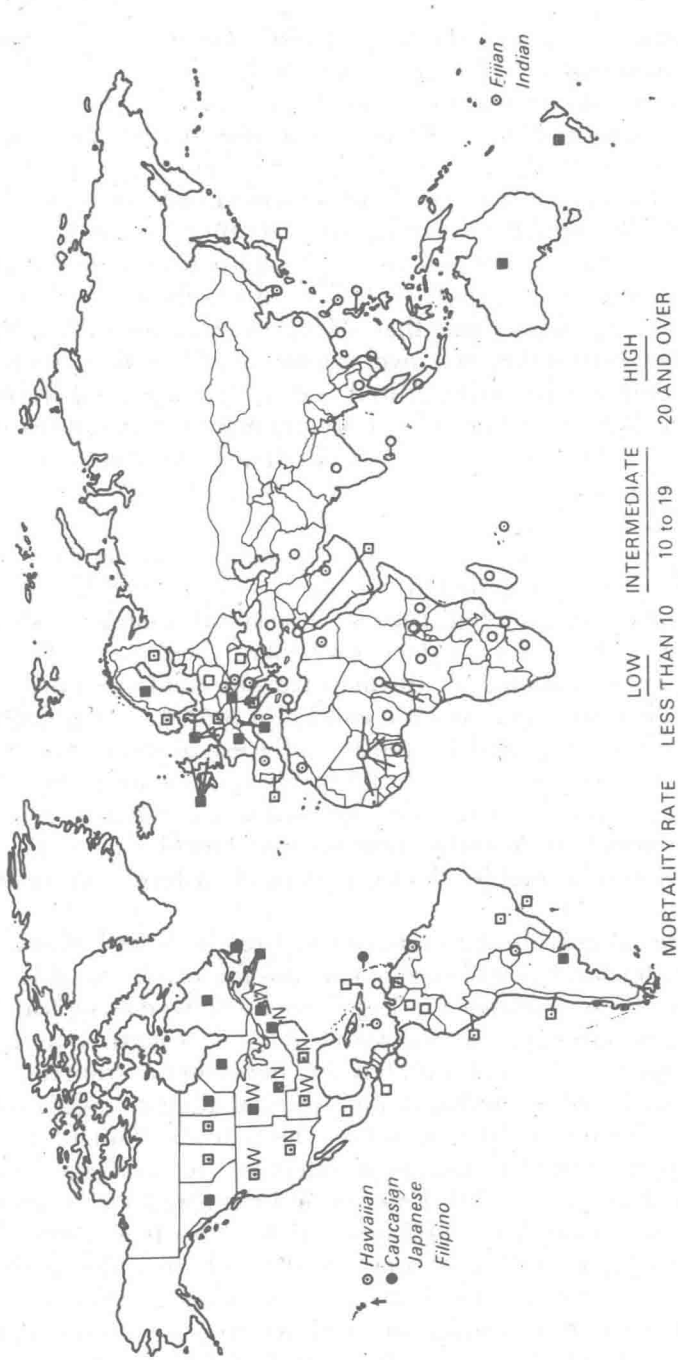

FIG. 2. World map of risks for cancer of the colon and rectum among males. Source: Dunham and Bailar (1968).

mation based on sources available as of 1967 agrees in most respects with the picture portrayed by the incidence data.

The mortality data for most of the west European countries (Austria, Denmark, England and Wales, France, Germany, Switzerland) appear to be consistent with the general characterization of this part of the world by the incidence data as a high-to-intermediate risk zone. However, it should be noted that the mortality data collected by Segi have consistently described Scotland to be a high-risk population. Doll (1969) considered Scotland to have the world's highest bowel cancer rate, certainly much higher than that of England, and Berg (1972) after review of the distribution of bowel cancer deaths within Scotland commented that, unlike in the United States, Denmark, and Norway, bowel cancer did not appear to be a predominantly urban disease in Scotland. The highest rates were in predominantly rural counties, 7 of which formed a contiguous band across north-central Scotland.

Dunham and Bailar were unable to secure much detail on the status of the Balkan and east European countries, but the information at their disposal placed these populations in the low-to-intermediate range. The establishment of more registries in these countries and the steady accumulation of new incidence data now confirm the presence there of relatively low risks, although for the most part the incidence rates tend to be higher than in Asian, African, and Latin American populations. The low incidence reported by the recently established registry in Zaragoza, Spain is consistent with the scanty relative frequency data for the Iberian peninsula assembled by Dunham and Bailar, and the collective information strongly suggests that bowel cancer risk in Spain more closely resembles the experience of eastern than western Europe.

All the tumor registries in Asia have consistently described low incidence rates for large-bowel carcinoma, and the results for selected registries from these continents in Fig. 1 can be viewed as typical. No populations with rates approaching those attained in North America or western Europe have been pinpointed, and the evidence from relative frequency data based on necropsy and hospital admission data coincide closely with the registry findings. The two population outliers with risks approaching the European intermediate level are Israeli Jews born in Europe or North America and the Singapore Chinese. The environmental exposures and food habits of the Israeli probably reflect their earlier experience abroad more closely than their current life-style in Israel. The contrast between Israelis born in North Africa or Asia and those born in Europe or North America is substantial, the bowel cancer risks for the latter being roughly 2.5 times greater.

The two African registries included in Fig. 1 rank close to the bottom of the list in magnitude of bowel cancer rates. These findings are consistent with those reported for the South African Bantu by Higginson and Oettlé (1960). The relative frequency data of Dunham and Bailar uniformly describe very low risks for Africa south of the Sahara and suggest no more than low-to-intermediate risks for African countries bordering on the Mediterranean.

Latin America presents a more heterogeneous pattern of bowel cancer risks than Africa or Asia. While many Latin American populations (Cali, Colombia; Recife, Brazil) display low rates comparable to those encountered in Africa and Asia, other populations appear to be at higher risk. The inter-American study of mortality (Puffer and Griffith, 1967) reported bowel cancer mortality in La Plata, Argentina to be only slightly less than that in San Francisco, California and Bristol, England, and the same source described intermediate rates for São Paulo and Ribeirão Prêto in Brazil (see Table I). The relative frequency data of Dunham and Bailar depict intermediate risks for Paraguay, and the collective information suggests a zone of intermediate to high bowel cancer risk extending from southern Brazil to Uruguay, Paraguay, and Argentina. The risk in the São Paulo area may be even higher than indicated by the reported data. There has been substantial migration from poverty-stricken, northeast Brazil (which the Recife data suggest to be a low-risk area) to the São Paulo

TABLE I
AGE-ADJUSTED MORTALITY RATES PER 100,000 POPULATION FOR CANCER OF THE LARGE BOWEL IN 12 CITIES[a]

City (country)	Bowel cancer (ICD 153–154)
San Francisco (United States)	13.0
Bristol (England)	12.9
La Plata (Argentina)	12.6
São Paulo (Brazil)	7.1
Santiago (Chile)	6.8
Ribeirão Prêto (Brazil)	6.4
Lima (Peru)	6.0
Caracas (Venezuela)	5.6
Mexico City (Mexico)	4.0
Guatemala City (Guatemala)	3.6
Bogotá (Colombia)	3.4
Cali (Colombia)	3.3

[a] Source: Puffer and Griffith (1967).

region, and the presence of a low-risk migrant population may have depressed the rates reported for São Paulo. Future studies should determine whether the São Paulo rate represents an average of a high risk among natives and a low rate for recent migrants.

The available information on operations and completeness of case coverage of the several registries would contraindicate interpretation of the findings as due solely to differences in diagnostic and medical care facilities. While the adequacy of diagnostic and medical care facilities vary, they seem unlikely to account for differences of the magnitude observed. The more recent incidence data collected by newly established tumor registries are important in elaborating and confirming earlier impressions from relative frequency presentations of necropsy and hospital admission data on striking geographical differences in bowel cancer risks.

B. Colon–Rectum Ratios

Inspection of Fig. 1 suggests a rough parallelism in the separate population rankings by order of risk for cancer of the colon and rectum, although the ranking for rectum deviates in some respects from the pattern presented for colon. The variation in rectal cancer incidence among the high-risk populations of North America and western Europe falls into a narrower range than does that for colon. While the lower colon cancer incidences in eastern Europe, Asia, Africa, and Latin America have their counterparts in lower rectal cancer rates, the internal relationships between colon and rectal cancer incidence rates become more variable in the latter populations. Despite obvious exceptions for individual registries the graph of the joint distribution of rates for colon and rectum for 28 registries in 26 countries (Fig. 3) reveals a strong correlation in the incidence rates for the two conventional subdivisions of the large bowel. A significant feature of Fig. 3 is the sex difference in the relationship between the incidence rates for colon and rectum. Females show a steeper rise in colon incidence for each unit increase in rectum incidence, the slope of the female regression curve being estimated as 1.72, substantially in excess of the slope estimate of 1.26 for males.

Discordances or systematic differences in the relationships of incidence for the two localizations can be simply expressed as colon–rectum ratios. The colon–rectum ratios of age-adjusted incidence for selected registries are given in Fig. 4. The greater female slope values for the regression of colon against rectal cancer incidence implies the presence of higher colon–rectum ratios for females in populations at

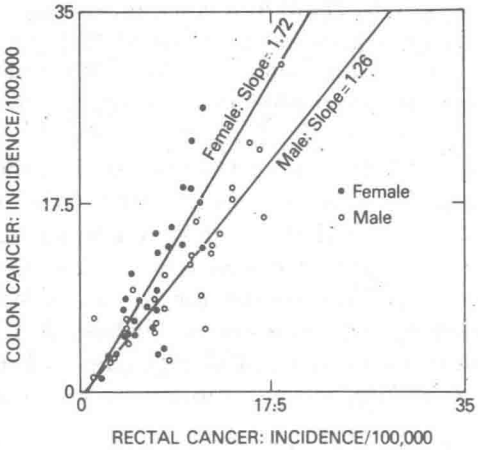

FIG. 3. Joint distribution of age-adjusted incidence rates for cancer of the colon and rectum, by sex. Selected registries, variable periods close to 1970. Source: Waterhouse *et al.* (1976).

high-risk to bowel cancer, and this feature is well expressed in Fig. 4. The Connecticut and the Hawaiian Japanese results are typical of those for North America. The registries in western Europe present more variable colon–rectum ratios. The results for Sweden, which are

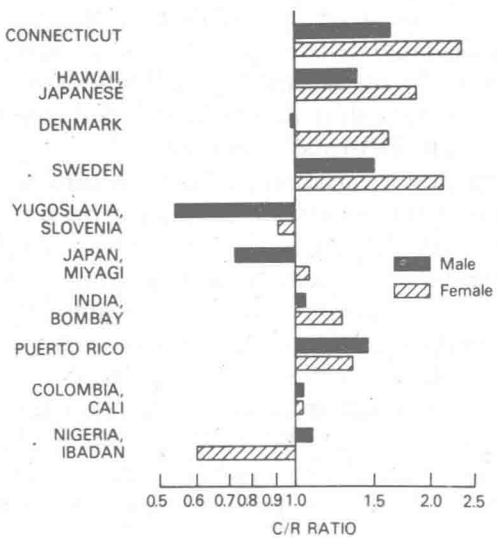

FIG. 4. Colon–rectum (C/R) ratios of age-adjusted incidence rates, by sex. Selected registries, variable periods close to 1970. Source: Waterhouse *et al.* (1976).