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Colorectal Cancer

Edited by William Duncan

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Preface

Colorectal cancer was the subject of the Third Symposium on Clinical Oncology organized by the Royal College of Radiologists, London, in February 1981. This publication of collected papers is based on the presentations at that meeting.

The purpose of these symposia is to encourage a multidisciplinary approach to our understanding and management of cancer. They bring together not only clinicians of different specialitics, but also non-clinical scientists who also have made a significant contribution both to basic knowledge and to applications of direct clinical relevance. It is hoped that symposia of this kind will be a stimulus to increasing collaborative research.

Colorectal cancer is now one of the most important causes of cancer deaths. The incidence of the disease varies greatly throughout the world but is particularly common in North America, Canada, and Western Europe. The aetiology of colorectal cancer is reviewed and a clear description is given of the factors associated with its high incidence in affluent Western societies. There is still no evidence of a direct association between dietary constituents and colorectal cancer, and so changes in our dietary habits that might help to reduce the incidence of this disease cannot be advised. While research in this important field continues, improvements must be sought in techniques of early diagnosis, assessment and management. It is particularly in the assessment and management of patients with cancer that the advantages of a multidisciplinary approach are generally recognized. In the field of colorectal cancer much remains to be done to confirm the benefits that are claimed to be associated with many new programmes of combined management. The results of surgical techniques have shown a small but appreciable improvement over the last 25 years. Further improvements in survival rates will be the results of more rational selection of patients with potentially curable cancer for specific regimens of combined management. Experience has shown that substantial progress can be achieved only by the scientific evaluation of carefully designed, strictly conducted, randomly controlled trials. It seems that increasing numbers of surgeons throughout the world are prepared to subject their results to peer review and audit, and to accept the demanding discipline of multidisciplinary controlled trials. Such collaboration must lead to steady improvements in the definitive management of patients with colorectal cancer. It is hoped that this publication may encourage greater participation in these clinical studies.

I have to express my thanks to those who presented papers at the Symposium, all acknowledged experts in their fields, and to their colleagues who contributed to the published papers in this volume. I would also thank Mr Michael Jackson of Springer-Verlag for his advice and patient co-operation, and Ms Dodsworth and other members of the editorial staff who have helped in the prompt production of these proceedings.

My thanks also go to Mr A.J.Cowles, General Secretary of the Royal College of Radiologists, and his staff, who helped in the excellent organization of the meeting in London.

And finally, the able assistance of my secretary, Mrs Joyce Young, has to be acknowledged, who once again undertook much of the work of organization of the Symposium and of completing the manuscripts for publication.

Royal College of Radiologists, London William Duncan

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Recent Trends

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Incidence

Geographical Variation

For some years the international scientific community has been engaged in filling some of the major gaps in our knowledge of the world distribution of cancer. This effort was coordinated originally by the International Union Against Cancer and recently by the International Agency for Research on Cancer. Collaboration between these organizations and a network of cancer registries throughout the world has led to a

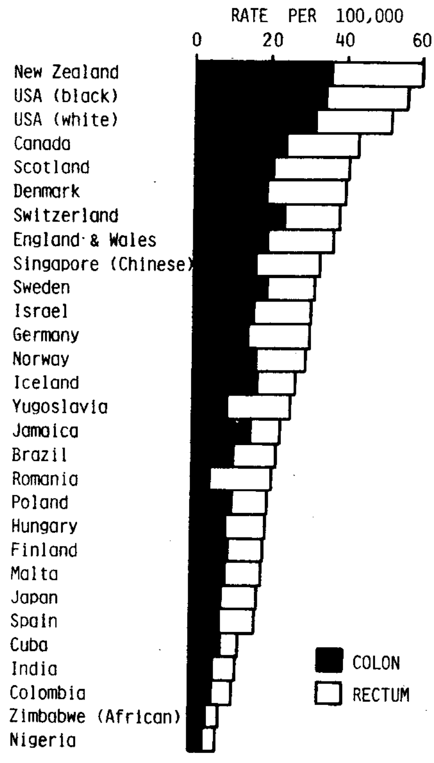

Fig. 1. Incidence of colorectal cancer: age-standardized rates per 100,000 males aged 35–64 in 1968–1972

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series of publications entitled *Cancer Incidence in Five Continents*. The third and most recent volume (International Agency for Research on Cancer 1976) contains information on cancer incidence in 28 countries covering the time period 1968–1972. Hardly any investigator making inter-population comparisons in cancer epidemiology in recent times fails to make use of this valuable source of information. It has been used here to demonstrate the geographical variation in the incidence of colorectal cancer (Fig. 1).

The highest incidence is reported by cancer registries in New Zealand, the United States, Canada, and Scotland, while rates are generally low in Africa, Asia, and South America. The European registries assume an intermediate position, though Western Europe and Scandinavia generally have higher rates than Eastern Europe and the Balkans. Although it is predominantly a disease of developed countries Japan presents an exception, being a highly industrialized nation with a low incidence of large-bowel cancer.

In Fig. 1 the male incidence rates for colorectal cancer have been arranged in descending order of magnitude. A representative figure has been calculated when a country has data from more than one registry. The rates have been adjusted to permit a valid comparison between populations with differing age structures. They have also been restricted to a comparison of incidence at ages 35–64, to remove the distortion in rates which may occur with under-reporting in the older age groups, the degree of which may vary between countries.

The incidence rates show a nine-fold difference between Nigeria, represented by data from Ibadan, and New Zealand, where a national registration scheme covers the whole country. The very high rates in New Zealand are not shared by the small Maori population. The contrast between the American negroes, who now have an incidence of large-bowel cancer comparable to that of caucasians, and the low rates in West Africa, from where many of their forefathers came some seven generations ago, emphasizes the importance of environmental factors in the aetiology of the disease (Burkitt 1971).

For neoplasms of the caecum to the descending colon and of the lower rectum, a fair degree of reliability can be placed on the localization as stated by the radiologist or surgeon. By contrast, it may be very difficult to decide whether a neoplasm has arisen in the lower part of the sigmoid colon or at the rectosigmoid junction. A sigmoid lesion is classified according to the 8th revision of the International Classification of diseases (Word Health Organization 1967) with other colonic neoplasms as 153, whereas a tumour arising at the rectosigmoid junction is classified with the rest of the rectum as 154. Most registries follow the International Classification of Diseases and include the rectosigmoid junction as part of the rectum.

Rectosigmoid lesions may account for 15%–25% of rectal cancers in high-risk populations (Correa and Haenszel 1978), so it is apparent that diagnostic difficulties, local custom in coding practice, and some looseness of definition could give rise to spurious differences between populations when cancers of the colon and rectum are considered separately. However, in examining this problem in six selected registries recording tumours of the rectosigmoid junction separately, de Jong et al. (1972) showed that inclusion of cancers of the rectosigmoid with the colon, rather than with the rectum, resulted in only minor changes in the incidence rates. Classification artefacts are therefore an unlikely explanation of the pattern of incidence shown in Fig. 1 when the age-standardized rates for large bowel cancer are subdivided into those of the colon and those of the rectum including the rectosigmoid junction. There is a strong correlation in the incidence rates for these two conventional subdivisions of the large bowel, and, with a few obvious exceptions the colon-rectum ratios are close to unity. Lower ratios are seen in Romania and Yugoslavia due to a deficit of colon cancer, and the opposite extreme is represented by Jamaica, where colon cancer is twice as common as cancer of the rectum. Switzerland and countries with a very high incidence of large bowel cancer overall also have higher rates for colon cancer. The incidence of colon cancer closely parallels the prevalence of adenomatous polyps in all populations so far studied (Correa and Haenszel 1978). The collective evidence supports the view that an adenomatous polyp is a precursor of the majority of cases of colon cancer. Inherited disorders, such as familial polyposis coli, which if left untreated invariably results in cancer of the large bowel, and malignancy secondary to colonic inflammatory disease account for only a small fraction of cases.

Subsite Distribution

De Jong et al. (1972) made a detailed examination of the subsite distribution of large bowel cancer in 12 selected registries. They showed that although the incidence of large bowel cancer as a whole varied by a factor of up to 6 in their data, the pattern of cancers throughout the large bowel was similar in different populations. The pattern is illustrated in Fig. 2 with data from the South Metropolitan (now the South Thames) Cancer Registry (International Agency for Research on Cancer 1976). There is a gradual fall in incidence from the caecum and ascending colon (153.0) through the transverse colon (153.1) to the descending colon (153.2), with a sharp increase in incidence for the sigmoid colon (153.3). The rate for the rectum (154.1) is higher than that for the sigmoid, and the incidence of tumours of the rectosigmoid junction (154.0) and anal canal (154.2) is low. This subsite distribution is typical of large bowel cancer in areas of high and intermediate risk. A more uniform distribution of incidence by bowel segment is a feature of low-risk populations. When cancer registries are ranked in order of large bowel cancer incidence, there is a rise in sigmoid-caecum ratios as one progresses from low- to high-risk populations (Correa and Haenszel 1978). Although the regular relationship between the subsite incidences in different countries suggests a basic aetiology common to all subsite cancers, there are instances where a selective increase at one subsite argues for a site-specific carcinogen. For example,

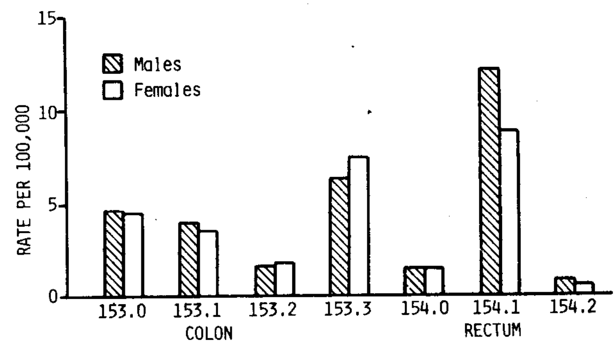

Fig. 2. Incidence of colorectal cancer by subsite from SMCR: age-standardized rates per 100,000 population aged 35–64 in 1967–1971

Denmark has a strikingly high incidence of cancer of the lower rectum despite intermediate rates for all other subsites (de Jong et al. 1972), and attention has been drawn to the relative increase in sigmoid cancer risk in Japanese migrants to Hawaii (Haenszel and Correa 1971). These segment-specific differences raise the interesting question as to whether large-bowel cancer represents a single disease or several diseases with different causes.

Sex Differences

Female incidence rates exhibit a similar ranking but a lower incidence of large bowel cancer overall, because rectal cancer is generally less common than in males. This is demonstrated in the male-female ratios in Fig. 3; in Fig. 3b few ratios are less than unity and male rates are on average 25% higher. Male dominance is also observed in colon cancer (Fig. 3a), though male-female ratios below unity are seen more frequently. Scotland, with a ratio of 0.74, shows the largest female excess.

Mortality

International Time Trends

Although 28 countries are now covered by cancer registries providing reliable data on incidence, an even larger number of countries compile mortality statistics for the major cancer sites. The World Health Organization has made these data readily available through the provision of computer tapes containing cancer mortality statistics for 33 countries since 1955. Although differences in treatment facilities and death

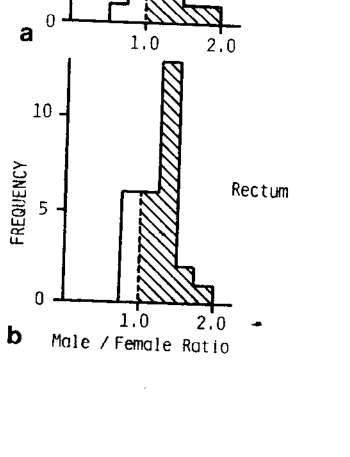

Fig. 3. Sex differences in cancer of the colon (**a**) and rectum (**b**)

certification practices will contribute to inter-country differences in mortality, the geographical distribution of mortality from colorectal cancer is consistent with the pattern of incidence (Correa and Haenszel 1978). These data from the World Health Organization enable us to examine time trends in mortality from large-bowel cancer in different countries over several decades. Selected examples are given in Table 1, the population of England and Wales in 1971 being used as the standard calculation of the age-standardized death rates.

A number of quite dissimilar international trends in mortality from colon cancer have been observed. Death rates in England and Wales are lower now in both sexes than they were 25 years ago. In Scotland death rates have also fallen, although the decrease has been relatively slow in recent years. With the exception of cancers of the lung and bronchus, colon cancer still causes more deaths in Scotland than any other cancer (Calman and Kemp 1976). By contrast, mortality in both sexes has increased in several European countries, the trends in Belgium and Czechoslovakia providing examples. Mortality has increased markedly in Israel and the Far East, particularly in Japan.

In many countries, including England and Wales, there has been a downward trend in mortality from cancer of the rectum. Scotland, however, has seen very little overall change, a fall in both male and female rates up to 74 years being compensated to a large extent by a rise in the older age group (Calman and Kemp 1976). Denmark had for many years held the leading place in mortality from cancer of the rectum in both sexes, but sharing in the decline, it has now been surpassed by Czechoslovakia, where mortality from rectal cancer is increasing. As a result of declining rates in the United States and increasing rates in Japan mortality from cancer of the rectum has become almost equal in these two countries, in sharp contrast with their very dissimilar levels of mortality from colon cancer (Logan 1976).

These diverse trends defy summary or easy explanation but must be the result of many factors acting in different directions and to varying degrees upon the different sexes and on different age groups and cohorts in the different countries.

Table 1. Mortality trends in selected countries: Age-standardised rates per 100,000 in 1955, 1965, and 1975

Country	Colon						Rectum					
	Male			Female			Male			Female		
	1955	1965	1975	1955	1965	1975	1955	1965	1975	1955	1965	1975
England and Wales	19.7	16.4	17.1	28.4	24.0	24.0	16.0	13.3	13.1	12.1	10.9	10.9
Scotland	29.0	22.0	21.6	39.2	30.9	29.4	15.7	11.9	13.1	9.8	11.1	9.7
Belgium	13.5	16.3	17.6	21.6	24.1	24.5	14.9	13.7	11.5	13.0	12.1	9.4
Czechoslovakia	8.6	10.3	14.5[a]	10.0	10.9	13.9[a]	11.2	13.2	16.8[a]	8.5	9.8	13.5[a]
Denmark	16.8	19.1	17.4	27.2	28.1	25.6	17.6	15.7	13.8	13.2	13.8	11.1
Israel	6.3	10.2	12.9[b]	7.4	15.1	17.6[b]	7.5	5.1	5.5	3.8	5.1	6.4
Japan	3.1	4.3	6.9	4.2	5.9	8.1	6.0	6.9	8.1	5.7	6.8	7.7

[a] 1974
[b] 1972

Mortality in England and Wales

Time Trends by Age and Sex. The standardized rates considered so far provide a convenient summary measure of the experience of a population as a whole. Figure 4 shows instead the trends in four 10-year age groups in male mortality from cancers of the colon and rectum in England and Wales during the last 50 years. In all but the oldest age group the death rates for both cancers were very similar 50 years ago. Mortality from both decreased appreciably after World War II but the decline has been more marked for rectal cancer. Now, roughly speaking, one person in five in England and Wales dies of cancer, and one in eight of these dies of large bowel cancer. Because of a slight increase in male mortality from colon cancer since the mid-1960s, apparent in all the age groups shown in Fig. 4, the colon-rectum ratios have increased in recent years (Officie of Population Censuses and Surveys 1978a).
Female age-specific death rates show a similar postwar decline in mortality from both cancers, but female mortality from colon cancer has not increased recently. Male mortality from colon cancer increases more steeply with age, so that whereas female rates are generally higher below the age of 65, male rates are higher in the older age groups. Female death rates for cancer of the rectum are lower than the corresponding male rates at all ages, and in all but the oldest age group female mortality has been declining steadily over the last 50 years.

Migrants. Migration from Scotland and Ireland and an influx of immigrants principally from Eastern Europe, the West Indies, and the Indian subcontinent have resulted in a substantial number of deaths in England and Wales among persons who were born elsewhere. The unshaded standardized mortality ratios (SMRs) shown in Fig. 5 compare the mortality from colon cancer among male immigrants with the mortality

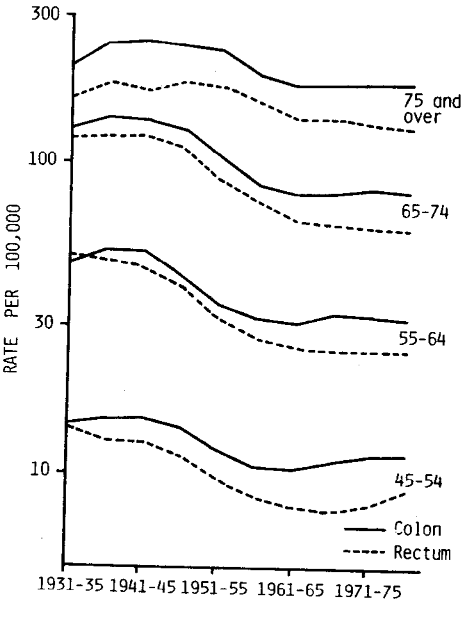

Fig. 4. Age distribution of male mortality from colorectal cancer in England and Wales in 1931–1978

experienced by the male population of England and Wales as a whole (Office of Population Censuses and Surveys, unpublished data). A ratio greater than 100 implies higher mortality among the immigrants and a ratio less than 100, lower mortality. The shaded SMRs similarly compare the mortality in the countries of origin with mortality in England and Wales. Mortality in the Indian subcontinent has been estimated from cancer registration data in Bombay because reliable mortality statistics are not available.

Studies of migrant populations, particularly in the United States and Australia, have shown that in general death rates from large-bowel cancer among immigrants tend towards those of the host population (Correa and Haenszel 1978). This trend is seen here for colon cancer, where mortality is tending to increase in male immigrants from lower-risk areas, such as India and Pakistan and Poland, and to decrease in Irish and American immigrants from higher-risk areas. The inference is that environmental factors, which may change on migration, are important in the causation of the disease. Mortality from colon cancer among female immigrants from low-risk areas shows a similar pattern, including an increase in mortality among West Indian women, although the data shown in Fig. 5 for West Indian males are not consistent with this hypothesis.

Regional Variation. In almost every country where regional studies have been carried out wide differences have been found in local levels of mortality. Regional differences between the standard regions of England and Wales have been summarized recently in *Area Mortality, 1969–1973* (Office of Population Censuses and Surveys 1981). In both sexes mortality from colon cancer is above average in the north-west region (male SMR 109, female SMR 107). In the West Midlands (SMR 103) and the north of England (SMR 107) only males show an excess. Mortality is particularly high in the large conurbations in these regions. Wales, outside the south-east, has higher mortality in both sexes (SMR 106) than eastern and southern England, where the SMRs range from 102 to 95.

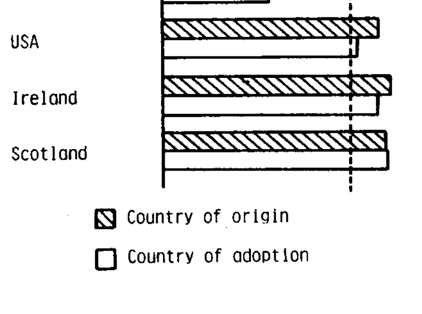

Fig. 5. Mortality from colon cancer among male immigrants in England and Wales in 1970–1972

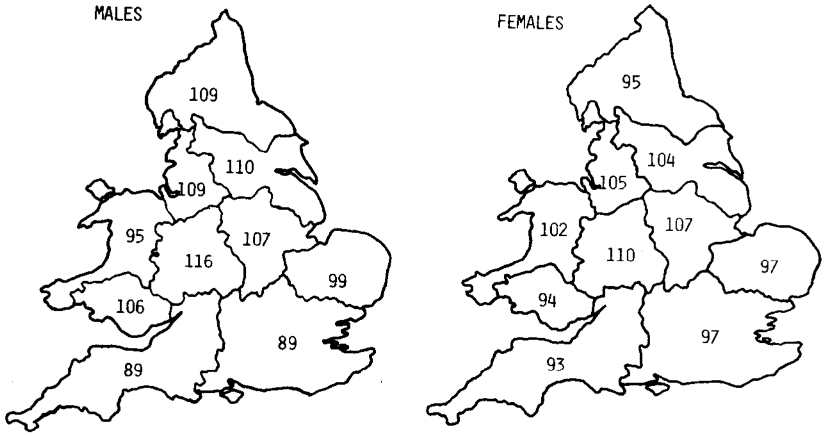

Fig. 6. Regional distribution of cancer of the rectum: standardized mortality ratios in 1969–1973

Cancer of the rectum shows greater regional variability in mortality than colon cancer (Fig. 6). Mortality is highest in the West Midlands in both sexes (male SMR 116, female SMR 110) and above average in north-west England (male SMR 109, female SMR 105) and the East Midlands (SMR in both sexes 107). Mortality is high only in males in Yorkshire and Humberside (SMR 110) and in the north (SMR 109). Dissimilar mortality patterns are also seen in the two sexes in Wales. Male mortality is above average in the south-east (SMR 106) but low in the rest of Wales (SMR 95), whereas the SMRs for females are 94 and 102, respectively. As with colon cancer, East Anglia and southern England experience a more favourable level of mortality, with SMRs of less than 100.

Mortality from colorectal cancer is higher in conurbations and densely populated urban areas than in smaller towns and rural districts, but the urban-rural differences are modest, rectal cancer again showing slightly greater variation with SMRs ranging from 107 to 94.

Social Class and Occupation. Male mortality from cancer of the rectum exhibits a social class gradient with higher mortality in the lower social classes, but male social class differences in colon cancer are small, mortality in social class V being only slightly higher (Fig. 7) (Office of Population Censuses and Surveys 1978b). Conventionally, the social class of married women is determined by their husbands' occupation. When classified in this way mortality from cancer of the rectum in married women shows a similar social class differential to that seen in men, with SMRs of 105 and above in the three manual classes. However, mortality from colon cancer is higher not only among married women in these three lower social classes (SMRs of 110 and above) but also in social class I (SMR 119).

Colorectal cancers are amongst the commonest tumours for which there is no clear evidence of a specific occupational factor. However, the *1970–1972 Decennial*

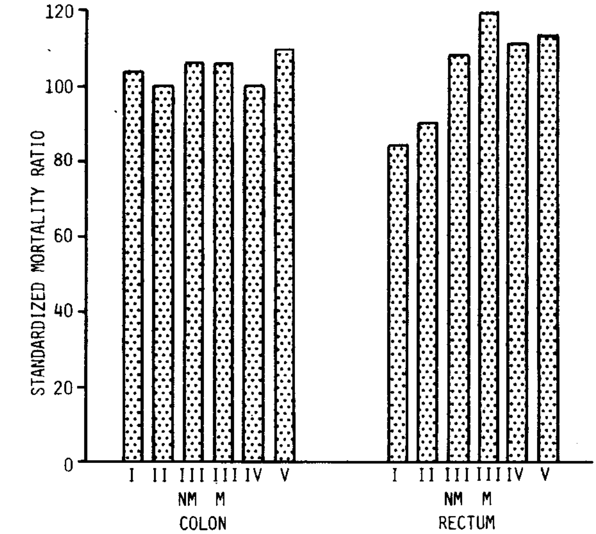

Fig. 7. Male mortality from colorectal cancer by site and social class at ages 15–64 in 1970–1972

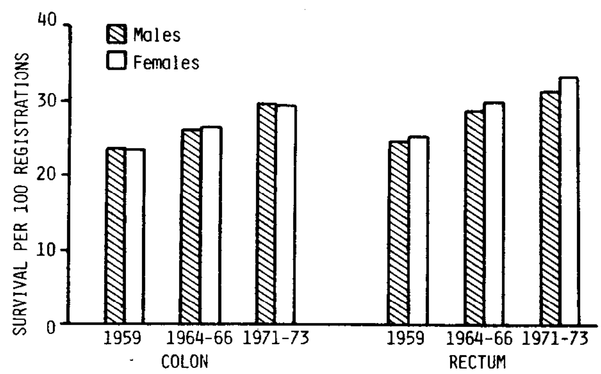

Fig. 8. Five-year relative survival (%) by sex and site of patients of colorectal cancer registered in 1959, 1964–1966, and 1971–1973

Supplement on Occupational Mortality (Office of Population Censuses and Surveys 1978b) reported high mortality rates for colon cancer in farm employers and managers (SMR 150) and for agricultural workers (SMR 136) but low rates for farmers working on their own account (SMR 69). Slightly higher mortality from rectal cancer was observed among engineering and allied trades workers (SMR 118).

Survival Data

Advances in treatment since World War II have improved the prospects for survival in patients with colorectal cancer. This is reflected in the steep decline in mortality in the post-war years when, for example, under antibiotic cover patients were able to withstand major surgery. Recent cancer registration statistics for England and Wales in 1971–1973 suggest that the prognosis for patients with colorectal cancer is still slowly improving (Office of Population Censuses and Surveys 1980).

The 5-year survival of patients with colon cancer increased between 1959 and 1964–1966 and increased again between 1964–1966 and 1971–1973 (Fig. 8). Even so, only 30% of cases registered in the last period were still alive 5 years later. More complete follow-up since 1971, with the National Health Service Central Register, and exclusion of cases detected only at death, may also have contributed to the apparent improvement in prognosis for colon cancer recently.

The prognosis for rectal cancer has also improved since 1959, so that over 30% of cases registered in 1971–1973 survived 5 years. By contrast with colon cancer, where survival is similar in both sexes, male patients with rectal cancer seem to fare less well than females. The prognosis for both cancers worsens with advancing age.

Conclusion

Recent trends in vital statistics relating to colorectal cancer reveal geographic, ethnic, and regional differences in the distribution of these cancers. They show changes in mortality over time and after migration, a higher risk in urban populations and the lower social classes, and generally higher mortality among males. The low rates of survival serve to emphasize that while clinicians are striving towards earlier diagnosis and more effective treatment, clues to aetiology, which may lead to prevention, must be vigorously pursued.

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Aetiology

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The descriptive epidemiology of colorectal cancer in England and Wales presented in some detail in Chapter 1 gives little clue to its aetiology. Its incidence shows that there are no marked differences according to social class or to region of the country, and no marked change over time. Few occupational associations have been reported apart from asbestos exposure, and this has not been a consistent observation. Moreover, the finding by Newhouse and Wagner (1969) that some peritoneal mesotheliomas in asbestos workers were misdiagnosed and described on death certificates as colon cancers raises further doubts about the association. Nevertheless, the marked international variation in incidence together with the much lower incidence among blacks in Africa than in those in the United States point to the importance of environmental factors in the causation of these cancers.

Genetic Factors

The most firmly established cause of colon cancer is genetic, namely the gene for polyposis coli. However, this is responsible for only a very small proportion of cases in the population, since only about 1 in 10,000 people are estimated to carry this gene. Several studies have observed an excess of colorectal cancer in the first-degree relatives of affected patients (see Table 1) which is apparently not explained by the inclusion of patients with familial polyposis coli.

Dietary Factors

Genetic factors, however, cannot explain the marked international variation in incidence shown by this neoplasm or why migrants from countries with a low

Table 1. Colorectal cancer in first-degree relatives of affected patients

Reference	Observed	Expected	O/E ratio
Woolf 1958	26	8.0	3.3
Macklin 1960	31	9.7	3.2
Lovett 1976	41	11.7	3.5
Bjelke 1980	23	13.7	1.7

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