Recent Results in Cancer Research 78

Prostate Cancer

Edited by William Duncan

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Fortschritte der Krebsforschung
Progrès dans les recherches sur le cancer

Preface

In February 1980 the Royal College of Radiologists, London, held its Second Symposium on Clinical Oncology. The subject was Prostatic Cancer and this publication is based on the presentations at this meeting by leading authorities in the United Kingdom.

The principal objective of these Symposia is to promote multidisciplinary collaboration for the benefit of cancer patients. Awareness and understanding of advances in a broad range of subjects are essential to ensure the timely and effective application of new techniques in the prevention and treatment of all forms of cancer. Communication of this kind may also stimulate the creation of new ideas that may prove to be of more fundamental relevance to cancer research.

Prostatic cancer has been afforded too little attention in the past, and its importance in Clinical Oncology has not been adequately recognised. And yet over the last 10 years considerable progress has been recorded in our understanding of this disease and in its assessment and management. These achievements are well documented in this collection of papers and the outstanding problems are also clearly indicated. It is acknowledged that the early diagnosis of prostatic cancer presents a continuing challenge, associated with the uncertainties that concern the clinical significance of 'latent' cancer of the prostate. The accurate assessment of the incidence and prevalence of the disease is extremely difficult and together these problems complicate the evaluation of the management of early or localised prostatic cancer.

There have been major developments in epidemiological, laboratory, and clinical research into prostatic cancer. There is now much better understanding of the form and function of the prostate and of its control. Considerable technical progress has been made in the assay of steroid receptors and in the refinement of tumour marker assay. Methods of imaging the prostate have greatly improved and nuclear medicine, particularly in the role of bone scintigraphy, is recognised to be of prime importance in the assessment of patients with prostatic cancer. Another great change in the last decade has been the increasing

use of radiotherapy in the primary management of patients with localised carcinoma of the prostate. Excellent long-term disease-free survival rates have been reported, and much more optimistic attitudes to the treatment of this disease have resulted. The administration of oestrogens is now advised for much more limited clinical indications following a series of extremely well-designed and carefully conducted clinical trials; their routine use for localised cancer of the prostate can no longer be regarded as an acceptable policy.

These developments are well reviewed in this volume and it is to be hoped that its publication may stimulate further interest in this fascinating disease. I have to express my gratitude to those who took part in the Symposium and also to their colleagues who have contributed to the texts for publication. I have also to record my appreciation to Mr. Michael Jackson of Springer-Verlag for his advice and understanding, and to his editorial staff who have helped to ensure prompt publication. My thanks are also extended to my personal secretary Mrs. Joyce Young, who ably assisted in the organisation of the Symposium as well as in the preparation of the scripts for publication.

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Epidemiology

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1 Introduction

This chapter reviews present knowledge of the aetiology of prostate cancer. Routine mortality and incidence statistics are examined both for England and Wales and for other countries, as are the results of a range of special studies. The chapter begins with a brief note on the problem of the diagnosis of prostate cancer, and its import as far as the validity of routine statistics is concerned. The review of aetiological studies does not result in any clear pointers to factors that could be avoided to achieve any marked effect on the incidence of this condition. Because of the relatively high toll of the disease it is important to consider whether any steps can be taken to reduce the delay prior to diagnosis and treatment. The chapter therefore ends with a brief consideration of the value of screening for this disease.

2 Validity of Routine Statistics

2.1 What is Prostate Cancer?

Morgagni (1760) demonstrated that suppression of urine could be caused by "preternatural swelling of the prostate gland"; he mentioned the type, social standing, and life habits of the patients. He was presumably referring to benign prostate hyperplasia, but it is worth considering the long history of concern about abnormalities of the prostate gland. Riches (1958) drew attention to the importance of the prostate as a site of malignant disease and suggested that it occurred in three rather different forms: latent, occult (with widespread metastases), and local definitive cancer. Rich (1935) reported 292 consecutive autopsies on males 50 years old and more; routine microscopical section identified 41 cases (14.0%) with frank carcinoma of the prostate, two-thirds of which were not recognised clinically. Edwards et al. (1953) examined sections of prostates from 173 consecutive autopsies in males 40 years and older, and 16.7% of the subjects were found to have a latent cancer of the prostate. Franks (1954) emphasised that latent cancer of the prostate was common and that its incidence increased with age; he suggested that the tumour has both morphological and

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biological characteristics of true malignancy, but lacks the capacity for rapid growth. In another contribution (Franks 1956) it was suggested that after the age of 80 the disease becomes common and over 90 years of age almost all men have these lesions (no hard data supporting this comment were provided). In an extensive study by Halpert et al. (1963) the prevalence increased with each successive decade of age. Scott et al. (1969) carried out step section at 4-mm intervals throughout the entire prostate for each of 158 males dying aged 70 and over. In 48% prostatic cancer was identified; this was twice the prevalence usually found at routine autopsy. The International Agency for Research in Cancer (Breslow et al. 1977) coordinated a study in which 50 prostates were collected from consecutive male autopsies in the age groups 45−, 55−, 65−, and 75+ from seven locations throughout the world. Duplicate readings were made by two pathologists in each case; and an exchange of opinions reduced the number of major differences in histological reporting. The frequency of small latent carcinoma was about 12% in all geographic areas involved. The distribution of larger latent carcinoma resembled that of clinical cancer, with a low frequency of latent carcinoma in two Chinese populations, an intermediate rate in Israelis and black Ugandans, and a high rate for German, Swedish, and black Jamaican populations. These findings agreed with those recorded in the more restricted groups studied in Japan (Karube 1961) and Hawaii (Akazaki and Stemmerman 1973).

Montgomery et al. (1961) followed up a small group of 35 patients with latent cancer of the prostate; after an average of nearly 7 years 24 of the subjects had died, but not one from prostate cancer. They suggest that specific treatment is not necessarily required when latent cancer is identified.

2.2 Some General Caveats

Mortality and routine incidence data are subject to a variety of errors and biases (see Alderson 1977). The mortality statistics are derived from death certificates stating that the prostate cancer was the underlying cause of death. Latent cancer, even if it has been diagnosed, will not be reflected in published mortality statistics if it does not contribute to the cause of death. If overt cancer is present, but the individual is thought to have died from some other disease, cancer may be mentioned on the certificate; at present multiple cause coding is not routinely published, and therefore one cannot tabulate statistics on the numbers of individuals having prostate cancer at the time of death.

The validity of the incidence data is rather different: whether the cancer is latent, occult, or overt, if it is recognised at some stage of the patient's treatment as being present it can be registered and reflected in the statistics. However, most probably only those prostate cancers investigated (and perhaps treated) are likely to be included in the registration statistics.

3 Mortality and Incidence Data

3.1 England and Wales

Figure 1 shows the age-specific mortality for England and Wales for 1973 and the incidence rates for 1970. The data are plotted on semi-log paper, and show a very steep

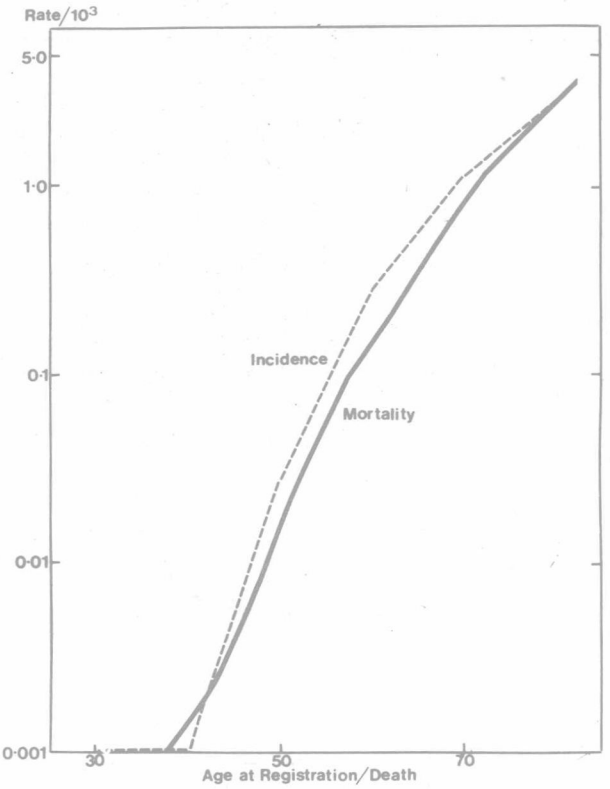

Fig. 1. Malignant neoplasm of prostate incidence rates, 1970, and mortality rates, 1973, by age at registration or death, England and Wales

rise in both incidence and mortality with advancing age. The other point to note is that the relative excess of incidence over mortality is very slight, indicating either that only a small proportion of subjects developing the disease are cured, or that the two sets of data are not equally valid. The excess mortality in the younger age groups is probably a reflection of small numbers, aggregation by age group, and differences in validity of the data.

Another way of looking at the age effect of this disease is to examine the cumulative frequency of distribution of deaths by age; such material is presented in Fig. 2 for England and Wales for the period 1971–1975. This shows how very few of the deaths occur in individuals under the age of 60, and that less than half the cases occur under the age of about 75.

Figure 3 shows the trends in mortality and incidence during the present century; five specific age groups have been selected, to reduce the number of lines on the graph. Data on mortality are available from 1911, but on incidence only since 1961. At the younger ages (i.e., up to 55–59) the mortality has not appreciably altered this century. For males aged 65–69 the mortality increased up until the 1930s but has since been relatively stable, whilst the mortality in males aged 75–79 increased fairly steadily up until about 1960 before levelling off. The incidence data are plotted for 10-year age groups and they are only available over a 13-year span (1961–1973). For the two older age groups there is a suggestion that the incidence is rising in the most recent material. Examination of these data plotted in different ways suggests that at least a proportion

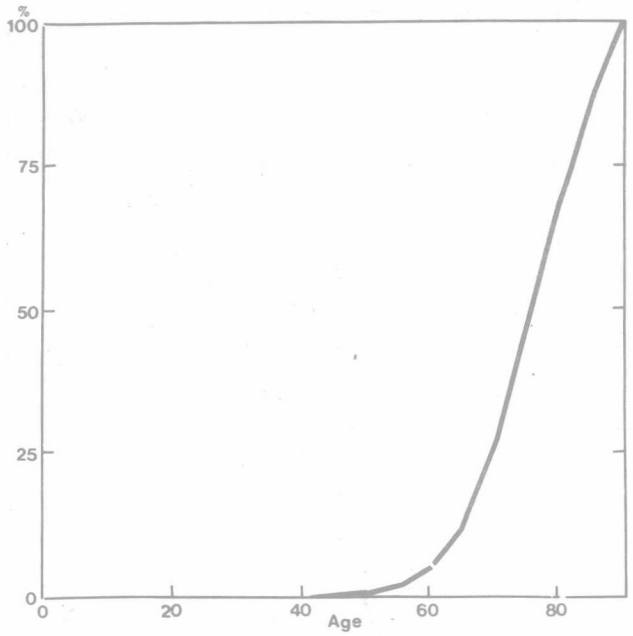

Fig. 2. Cumulative frequency distribution of deaths from malignant neoplasm of prostate in 1971–1975 by age, England and Wales

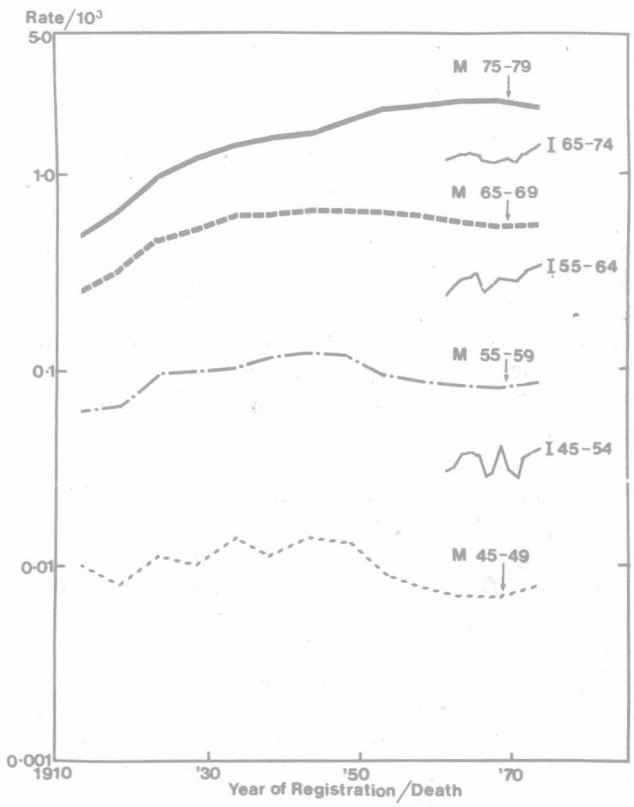

Fig. 3. Age-specific mortality rates for malignant neoplasm of prostate for 1911–1975 (*M*) and incidence rates for 1961–1973 (*I*), by year of registration or death, England and Wales

of the rise in the elderly is attributable to diagnostic factors rather than a general environmental factor or any difference in behaviour from one cohort to another.

3.2 International

In an attempt to examine the international variation in this disease and also any association with a cancer that is typical of 'Western' society, the age-specific mortality for cancer of the prostate against cancer of the lung was examined for 50 countries around 1976. There is considerable variation in the mortality rates for both conditions, with no suggestion of a relationship between the two. Even if an environmental factor is responsible for prostate cancer it has not spread in different countries in parallel with the development of smoking.

Other work has suggested a relationship between prostate cancer and sexual activity, and perhaps multiple consorts or acquisition of venereal disease (see Sect. 6). Data have been examined for cancer of the prostate and cancer of the cervix; unfortunately, however, the published mortality statistics for cancer of the cervix show that the proportion of cases ascribed to cervix cancer (compared with unspecified uterus cancer) varies markedly from one country to another. Both Hill (1975) and Weiss (1978) drew attention to the major problem in interpreting uterine cancer mortality, namely that cancer of the body of the uterus is frequently misclassified. Consideration of these points leads to the conclusion that it would be inappropriate to use national mortality statistics to seek a possible relationship between levels of cervix and prostate cancer.

Lancaster (1952) commented upon the increase in the death rate related to specifically male cancers in Australia over a relatively short period of time. Over the same time period there was no evident increase in the mortality from prostate hyperplasia and therefore no evidence that the increased incidence of cancer had been due to a shift in diagnosis. Ravich (1978) suggested that calculation of the incidence of this condition in Japan was unreliable; he ignored the method by which population incidence rates are normally calculated and compared.

Henschke et al. (1973) reviewed the mortality trends in the United States for 58 sites of cancer for whites and non-whites by sex, in the period 1950–1967. Prostate cancer was included in the group which had 'increased' significantly more slowly in the whites than blacks. After consideration of a number of defects in the data they suggested that 'environment' may be the main influence.

Ernster et al. (1978a) examined the cohort mortality for prostatic cancer amongst United States whites and non-whites. They showed a quite clear cohort mortality trend in the non-whites (but not for the whites). There were increasing rates of mortality in the cohorts born in 1846–1896 and then a complete reversal in the trend, with a decrease in age-specific mortality in the cohorts born after 1900. They concluded that alteration in medical care, screening, or accuracy of diagnosis is unlikely to have caused this picture, and that an aetiological factor had altered its impact on the non-whites in the United States in the groups born up to the beginning of the present century.

Jackson et al. (1975) report preliminary findings from a collaborative study in which data have been collected from patients with prostate cancer in the United States and Nigeria. They suggested that (i) the cancer is common in both United States and Nigerian blacks, and (ii) the Nigerian patients had less well-differentiated tumours,

with more numerous foci of cancer, and lesions that were at a later stage of presentation.
Tulinius (1977) examined the incidence and mortality from prostate cancer in data collected from a large number of countries (45 countries for mortality). He drew attention to the very sharp increase in the incidence of and mortality from this condition in the elderly and very elderly (in contrast to other cancers); he pointed out that as the proportion of elderly persons in any population rises there will be a particularly marked increase in the total number of prostate cancer patients.

4 Genetic Factors

Lynch et al. (1966) reported a family of seven siblings, five of whom developed histologically proven cancer. Three brothers had carcinoma of the prostate, and two of these had other primary cancers as well. These findings were compared with the material from 109 consecutive patients treated with cancer of the prostate; for only five of these (4.5%) was a first-degree relative with the same cancer reported.
An estimate of the rarity of family aggregations cannot readily be made from such reports.
Woolf (1960) traced the death certificates for parents and siblings of 228 subjects dying from carcinoma of the prostate; he compared the causes of death of the relatives with those of control subjects. Death from prostate cancer was about three times as frequent in the relatives of the index patients as in the controls ($p < 0.05$). Three case-control studies, examining a range of factors, found an excess of positive family histories in the prostate cancer cases (Steele et al. 1971; Krain 1974; Schumann et al. 1977). Thiessen (1974) compared the family histories of 145 women with breast cancer against results from age-matched controls. A significant excess of prostatic cancer (and also breast and uterus cancer) was reported in both maternal and paternal relatives.

4.1 Blood Group

Bourke and Griffin (1962) compared the blood group distribution of 224 prostate cancer patients with that of 10,000 controls; they found a significant excess of blood group A in the cancer patients, and those with blood group A were younger at diagnosis. No difference was found between subjects with benign prostatic hypertrophy and controls. Wynder et al. (1971), in an extensive case-control study, found no variation in blood group recorded between the prostate cancer patients and control subjects.

4.2 Ethnic Group

A number of authors have examined the prostate cancer mortality in the United States of foreign-born residents: Smith (1956) found this to be low for Japanese migrants; Haenszel (1961) found it to be reduced for whites from 12 different countries;

Haenszel and Kurihara (1968) found it reduced for Japanese; Staszewski and Haenszel (1965) found it to be low for Poles; King and Haenszel (1973) found it reduced for Chinese. Stemmerman (1970) suggested that metastatic prostatic cancer was uncommon in Japanese dying in Hawaii. Blair and Fraumeni (1978) observed that prostate cancer mortality was raised in states in the United States with a high percentage of residents from Scandinavia.

Using a variety of different approaches to examine the influence of ethnic groups on incidence or mortality from prostate cancer, Smith (1957) reported a markedly reduced mortality amongst Indians; Newill (1961) observed reduced mortality for Jews, with small differences for place of birth; Wynder et al. (1971) noted less risk of prostate cancer in immigrants from Eastern Europe; Mancuso and Stirling (1974) recorded no variation in prostate mortality for Ohio residents dying in 1959–1967 in relation to place of birth and migration within the United States; Ross et al. (1979), using cancer incidence data for Los Angeles, confirmed the very high incidence in blacks and amongst upper occupational and social class groupings.

Levine and Wilchinsky (1979) examined the stage at presentation and survival within stage of blacks versus whites. There was a significant excess of blacks with more regional and distant metastases; within stage, there was no difference for survival at 5, 10, or 15 years after treatment.

5 Association with Other Diseases

5.1 Benign Prostatic Hyperplasia

It is conceivable either that benign prostatic hypertrophy predisposes to malignant disease or that there is a factor responsible for increasing the risk of both benign and malignant disease of the prostate. The trends for mortality of these two conditions have been quite different since 1911 in England and Wales. There have been miscellaneous case reports, such as that by Guerrier and Persky (1969), who reported the association of leukaemia, hyperplasia, and carcinoma of the prostate in one patient. Armenian et al. (1974) found that there was a relative risk of 5.1 ($p < 0.001$) of finding benign prostatic hypertrophy in prostate cancer cases as against controls. In a prospective study of 345 patients with benign prostatic hypertrophy they found that the death rate from prostate cancer was 3.7 times greater following benign disease of the prostate than in the controls. However, these findings have been disputed: Franks (1974) suggested benign hypertrophy was so common it could not be directly responsible for the risk of cancer; Williams and Blackard (1974) and Rotkin (1975) felt the selection of cases and controls introduced bias in the quality of diagnosis and the use of death certificates was suspect.

Greenwald et al. (1974a) followed up over 800 patients with benign prostatic hyperplasia; there was no difference in the proportion of patients with benign hyperplasia and controls who subsequently developed prostate cancer. The British Medical Journal (1975) concluded that there was little reason to doubt the validity of the findings. Higgins (1975) suggested that latent cancers were likely to be eliminated because the benign cases were treated surgically while the controls were not (this may be a fallacious argument as resection for hyperplasia does not include the lateral lobes, in which cancer tends to occur).

5.2 Cirrhosis of the Liver

Robson (1964, 1966) examined the prevalence of prostatic cancer at autopsy of 205 patients with cirrhosis and in other autopsy subjects. A lower prevalence of prostatic cancer was found in those with severe liver disease, but no different in those patients with or without evidence of 'hyperoestrogenism'.

6 Association with Sexual Behaviour

King et al. (1963), in a lengthy review of the epidemiology of prostate cancer, concluded that sexual behaviour may be related to differences in mortality and morbidity and reflected in racial, regional, urban/rural and occupational differences.

Lancaster (1952), using mortality statistics from Australia with census data as the denominator, reported an excess of prostate cancer in married subjects who had children. A number of case-control studies have explored this issue. Wynder et al. (1971) suggested that there was no significant effect of marital status or fertility differentiating between the cases and controls. Steele et al. (1971) recorded greater extramarital activity, sexual drive, and frequency of venereal disease in the prostate cancer patients. Krain (1974) reported a significant excess of past history of venereal disease, increased coital frequency, increased number of sexual partners before marriage, and the use of contraceptive agents in the prostate cancer patients. He found no difference in the number of sexual partners after marriage. Greenwald et al. (1974b) found no difference in the marriage patterns of Harvard students subsequently dying from prostate cancer. Rotkin (1977) suggested that patients had (i) delayed sexual drive and development, (ii) repression of sexuality at the time sexual activities normally began, and (iii) a fall-off of sexuality early in adult life. No differences were found for the number of marriages or the number of sexual partners.

Schumann et al. (1977) noted a tendency amongst the prostate cancer patients for increased number of sexual partners (including prostitutes), reported prior venereal disease, and genital infections in the spouse. The age at first intercourse and first marriage was lower in the cancer patients, and the patients had higher fertility and more instances of prostate cancer among their relatives.

Greenwald et al. (1979) found no difference in the average duration of widowhood, and frequency of more than one marriage was the same for the patients with prostate cancer and controls. However, they did note an excess of breast cancer and endometrial cancer in the wives of the prostate cancer patients, though neither of these results was statistically significant.

Role of Viral Infection

One aspect of the sexual behaviour of the cases and controls is the possibility that this is associated with exposure to virus infection. Schumann et al. (1977) found slightly higher antibody titres for herpes and cytomegalic virus in prostate cancer patients than in controls. However, Ross et al. (1979) have suggested that descriptive and analytical