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Editorial

THE EPIDEMIOLOGY OF CANCER OF THE PROSTATE

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IN 1969, 16,836 men in the United States were reported as having died of cancer of the prostate. The mortality rate of 17.1 per 100,000 for this site was second only to that for cancer of the lung [1]. The American Cancer Society has estimated that 38,000 new cases of the disease are diagnosed each year [2]. Yet the cause of this common cancer is obscure and relatively few of the related factors are firmly established. Comprehensive reviews of the epidemiology of cancer of the prostate have been published [3, 4]. Certain facts are clear. Cancer of the prostate increases steadily with age from about 40 and is rare under 50 yr of age. There are large international differences both in incidence [5] and in mortality [6, 7]. Rates are high in the United States, particularly among negroes, but they are low in oriental peoples particularly among the Japanese in Japan. These low rates are largely confined to clinical cancer since autopsy data have shown that latent cancer is almost as frequent in Japanese as in Caucasian males of similar age [8–10]. Migration appears to influence the liability to the clinical disease. Japanese and Polish immigrants to the United States have higher death rates than Japanese and Poles in their native lands [11, 12]. The increased rates suggest that environmental factors not previously operative before emigration may be important. Migration may also possibly explain the association of cancer of the prostate with religion. The disease has long been known to be relatively uncommon in Jews [13]. A study of mortality in the three main religious groups in New York City for the years 1953–1958 [14] showed that the rates for Jews were 83 per cent of those for Catholics and only 64 per cent of those for Protestants. The recent study by Wynder and his colleagues [4] suggests that this association now holds only for men aged 70 and over. A high proportion of Jews in this age group in N.Y.C. came from Russia and Poland, countries where death rates from cancer of the prostate are low. Furthermore in Israel where mortality rates for this cancer are relatively low, the incidence is higher in Jews originating in Africa or Europe than in Jews from Asia or Jews born in Israel [15].

Cancer of the prostate appears to be fairly consistently related to marital status [3]. Mortality rates for cancer of the male genital organs (90 per cent of them prostate) are higher in the ever married than in single persons with the highest rates in the widowed and divorced. Furthermore there is a suggestion that the increased rates among the married may be mainly in those who have had children [16]. Mortality rates from prostatic cancer among priests are clearly of interest in this connection. No study appears to have been made. During the years 1949–1953 in England and Wales the Registrar General reported that two Roman Catholic priests aged 65 yr and over died

of cancer of the prostate whereas five would have been expected [17]. The relationship with marital status suggests that sexual factors may be important. To date there have been very few investigations of sexual practices in relation to cancer of the prostate. A comparison of a small number of cases with age matched controls [18], suggested that patients with prostatic cancer had a greater sexual drive as indicated by multiple sexual partners, extra-marital activity and frequency of venereal infection. Although doubt has been cast on the significance of sexual factors by recent studies [4, 19] the populations investigated were not ideal for demonstrating them. Further observations on sexual behavior in relation to cancer of the prostate are urgently needed.

Heredity may be important. A higher frequency of prostatic cancer in the relatives of patients with the disease than in the relatives of controls has been a consistent finding in those few studies which have looked into the question [20]. A higher frequency of blood group A in prostatic cancer cases has been reported [21] but has not been confirmed [4]. Prostatic cancer has often been found to be commoner in urban than in rural areas [3]. The reason for this is uncertain; but the observation in Buffalo that mortality was positively correlated with levels of total suspended particulates [22] suggests that air pollution may contribute. Mortality statistics by area from England and Wales [23] do not however provide much support for air pollution as a major factor in the disease. Socioeconomic circumstances are not consistently related to cancer of the prostate [24, 25] nor do occupational mortality statistics point to any occupational exposures. The higher rates sometimes noted in the professional classes probably reflect more accurate diagnosis. The suggestion that workers exposed to cadmium fumes [26, 27] may have an excess risk of developing this cancer however deserves to be followed up. Cancer of the prostate does not appear to be consistently related to prostatitis (though more information on infection is needed), calculus, circumcision, tobacco smoking or alcohol ingestion [4].

Cancer of the prostate is often thought of as a hormone-dependent cancer partly because of the experimental demonstration of regression following castration or estrogen therapy [28] and partly because of the finding at autopsy of multiple endocrine changes [29]. The correlation of cancer of the prostate with cancer of the breast has also been advanced in support for this view [30]. Although much of the biochemical evidence is contradictory, recent studies of urinary hormone metabolites in patients and healthy controls [31, 32] have shown that cancer cases excrete less androsterone, have a lower estrogen/etiocholanolone ratio and excrete a higher proportion of total estrogen as estrone and estradiol than control subjects. There does not however appear to be consistent differences in hormone levels between Americans and Japanese. Nor have studies which have included hair distribution as a measure of hormone levels revealed any consistent differences between cancer cases and controls [33]. A report that cancer of the prostate is less common at autopsy in patients with cirrhosis of the liver [34], a condition in which estrogen levels are high [35], may be of some significance in this connection.

The relationship of benign prostatic hyperplasia (BPH) to cancer of the prostate, is controversial. The two conditions are common, especially if latent prostatic cancer is included; both increase progressively with age. By chance therefore they will often be found to coexist. There have however been some indications that BPH may be a precursor of prostatic cancer [29]. Two epidemiological papers have recently described well-controlled investigations of the relationship between BPH and prostatic

cancer. Armenian and his colleagues [36] conducted both prospective and retrospective studies. In the prospective study, 345 patients with BPH but with no evidence of prostatic or other malignancies, who were admitted to Roswell Park Memorial Institute between 1945 and 1965 were identified. Seven incorrectly diagnosed cases were excluded and the remaining 338 cases were matched for age and time of admission with randomly selected patients discharged during the same period with a diagnosis of nonneoplastic disease. Cases and controls were followed until 31 December, 1972 through the case notes when these were complete and by searching for death certificates and cancer registry reports at the New York State Health Department for the remainder. Follow-up was equally complete for both groups, 87.6 per cent of the cases and 88.5 per cent of the controls being traced. The total number of person-years of follow-up was similar, 2540 for the cases and 2285 for the controls. The death rate from prostatic cancer among patients with BPH was 10.1 per 1000 person-years compared with 2.7 per 1000 person-years among the controls, giving a relative risk of 3.7 times greater among the BPH patients. Death rates in the study group were higher than the age adjusted rates for New York State in 1960. But the proportional mortality from prostatic cancer among the controls was similar to that for the State. Among those who underwent prostatectomy, prostatic cancer rates were 5.1 per 1000 person-years whereas among those who did not the rates were 11.3 per 1000 person-years, suggesting a considerable reduction in subsequent cancer risk from the operation.

In the retrospective study 290 patients with prostatic cancer were matched with 290 controls with a non-neoplastic final diagnosis. Matching was for age and period of admission (1957–1965). Information on previous admissions were copied from the records and coded, without knowledge of the diagnosis, for reason of admission and index of suspicion of cancer. One hundred and four of the cancer cases had previously been admitted for prostatic disease compared with only 27 of the controls. Sixteen of the BPH cases and one control were coded blindly as suspected prostatic cancer. One prostate-cancer patient had been previously admitted for prostatitis. A matched pair analysis on the remaining 87 possible BPH admissions among the cancer cases and 21 such admissions among the controls indicated a relative risk of 5.1 for prostatic cancer. This difference was not eliminated by considering different intervals between index and antecedent hospital admissions. Thus in both prospective and retrospective studies an increased risk of prostatic cancer from BPH was clearly shown.

These findings are at variance with a study carried out by Greenwald and his colleagues [37]. This was based on 838 men who had had subtotal prostatectomy at the Lahey Clinic Foundation, Boston, Mass. during the period 1940–1959. All were under 80 yr of age and histological examination had indicated prostatic hyperplasia with no evidence of malignancy. These patients were matched with men in the same 5-yr age group who had had surgery at the same time for some other condition but who had no known disease of the prostate or malignancy at the time of surgery. Follow-up was similar for both groups; 88 per cent of the cases and 91 per cent of the controls were followed to death or the termination of the study (31 December, 1970). Tracing was through review of clinic records, letters to patients, family members and physicians, supplemented when appropriate by examination of voting lists, city directories and similar sources. Diagnosis of prostatic cancer was based on hospital records, pathology reports, letters from physicians, copies of abstracts of death certificates and autopsy reports. Duration of follow-up was comparable for the two groups, 10.7 yr for the

cases and 11.2 yr for the controls, the small difference reflecting a slightly higher mortality among the BPH cases. Twenty-four (2.9 per cent) of the 835 BPH cases and 26 (3.2 per cent) of the 802 controls developed cancer of the prostate. No differences were found on analysis by specific 5-yr age groups. When the data were analyzed using a modified life table method 3.0 cases of prostatic cancer developed per 1000 person-years among the BPH group compared with 3.1 cases per 1000 person-years among the controls. The relative risk of prostatic cancer in the BPH group was estimated to be 0.88.

How can the discrepancy between these two groups of workers be explained? One obvious explanation is that the Lahey Clinic BPH group had been treated by prostatectomy which might be expected to reduce the risk of cancer and indeed was shown to do so by Armenian and his colleagues. But even in their prostatectomy group these workers noted an approximately twofold increased risk of cancer. It is possible that in their prospective study, patients with undetected cancer at entry may have been included among the BPH cases since R.P.M.I. is a cancer referral center. No information is given about the number of hyperplasia cases who were referred because of a suspicion of cancer. The possibility that the BPH patients had a greater chance of having prostatic cancer detected was however considered by these workers. Although this possibility could not be entirely eliminated, the authors considered it to be unlikely because of the reduction in risk shown to be associated with prostatectomy.

Bias could have been introduced into the study by Greenwald and his colleagues through the exclusion of cancer by histological examination of the excised prostates. By eliminating latent disease from their case group but not from their controls it seems possible that a twofold increase in risk of clinical cancer might have also been eliminated. It would be interesting to know what percentage of BPH prostatectomies were excluded because of latent cancer. Not only might this explain the discrepancy in the findings in these two studies, it might also afford a good opportunity for estimating the rate of progression of latent to clinical cancer, a point on which there is disagreement [38].

Armenian and his colleagues suggest a randomized controlled trial of the effect of prostatectomy in symptom-free patients with BPH who had additional epidemiologic characteristics associated with a high risk of prostate cancer. They estimate that if the prevalence of BPH in men over 50 is 30 per cent and the risk of cancer is 3.5 times greater in those with BPH, 43 per cent of all prostatic cancer may be attributed to BPH. Prophylactic prostatectomy in such cases should very materially reduce the incidence of this highly fatal form of cancer. Although potentially an extremely interesting study, one might anticipate a certain reluctance on the part of symptom-free patients to participate. The suggestion by Wynder and his colleagues that elucidation of the etiology of cancer of the prostate needs close team work of epidemiologists, pathologists, nutritional biochemists and steroid chemists concentrating particularly on the differences in clinical (and I might add latent) cancer in Caucasians, Negroes, native Japanese and immigrants to the U.S. should be heeded.

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