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PROSTATE CANCER IN NORTHERN SWEDEN

Incidence, survival and mortality in relation to tumour grade

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In order to study changes in incidence, survival and mortality of prostate cancer in relation to morphological grade, we analysed all incident cases of prostate cancer in Northern Sweden during three 2-year periods (1974–1975, 1980–1981 and 1986–1987). The age-adjusted incidence increased by 35% from 1974–1975 to 1986–1987, but there was only a minor increase in the mortality rates. The increase in incidence was mainly due to well-differentiated (G1) and moderately differentiated (G2) tumours, whereas the incidence of poorly differentiated (G3) tumours remained stable. The 5-year relative survival rate increased significantly from 1974–1975 to 1986–1987. The relative survival rate for each tumour grade was, however, almost stable over the studied time period. After adjustment for tumour grade the differences in relative survival rate diminished. We believe that the most likely explanation for these changes in incidence, survival and mortality is enhanced detection of tumours with more favourable histology as a result of a more frequent use of the diagnostic tools available.

It is well known that the reported incidence of prostate cancer (PC) has increased during the last decades both in Sweden and in other parts of the Western world. During the same time period the mortality rates for this disease have remained almost constant (1, 2). These diverging trends might theoretically be explained in several ways. One explanation for the increase in incidence might be exposure to risk factors for development of PC. This mechanism is suggested by migration and correlation studies from Hawaii and other parts of the US (3–5). Another reason could be changing reporting routines by the diagnostic laboratories, with an increasing tendency to report more borderline tumours. A third reason could be more extensive use of diagnostic tools, such as transurethral resection and transrectal fine-needle aspiration biopsy. Thus, prostate cancer may be latent and asymtomatic for many years and found only accidentally at a routine physical examination, transurethral resection or at autopsy (6). The diverging trends in incidence and mortality can be explained either by more successful treatment or by enhanced detection of non-fatal tumours that do not effect the mortality rate. Today we have little knowledge of which of these explanations is the most relevant.

The best-known prognostic factor for PC is the morphologic differentiation of the tumour (tumour grade) (7, 8). It might be expected that the factors discussed above would influence and change the distribution of tumour grade in a population. We therefore analysed trends in incidence, survival and mortality rates of prostate cancer in relation to the distribution of tumour grades, for cases of PC reported to the cancer registry for Northern Sweden during 1974–1987.

Material and Methods

All cases of adenocarcinoma of the prostate reported to the regional cancer register for Northern Sweden during the three 2-years periods 1974–1975, 1980–1981 and 1986–1987 were included in the study. A total of 2 618 cases were reported, with 685, 852 and 1 081 cases deriving

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from the three mentioned time periods respectively. The region encompasses a population of about 900 000 inhabitants and the age distribution was almost stable during the period studied. The incidence rates were derived from the regional cancer register in which also cases diagnosed only at autopsy are included. The mortality data from statistics Sweden was utilised. The coding habits in this register changed in 1980/81 and the mortality rates decreased slightly because of these changes (9). Previously cases reported on the death certificates with cancer as underlying or contributory cause of death were often coded as death with cancer as underlying cause of death according to the principle 'cancer takes over other diseases as cause of death'. From 1980/1981 the coding has been made according to the recommendations by WHO which means that prostate cancer more often has been coded as a 'contributory cause of death' with a corresponding reduction of cases coded as dead with prostate cancer as 'underlying cause of death'. Both incidence and mortality rates were age adjusted. Age standardisation was accomplished by the direct method, using the 1970 Swedish census population as reference.

Observed survival rate was calculated from the data concerning diagnosis and death in the cancer registry. The national standard population was used when calculating the expected survival rate. The relative survival rate (RSR) was then determined according to Hakulinen (10). The RSR is the ratio between the observed and expected survival rates. The RSR estimates the relative chance of surviving with PC. When adjusting RSR for tumour grade, the grade distribution in 1974–1975 was used as reference. Diagnoses made for the first time at autopsy were excluded from survival analysis. The end date for follow-up was February 1, 1991. Thus, the follow-up time for survival was 4–18 years. Differences in RSR were tested with the log-rank test.

The tumour grades for all cases were derived from the filed notification forms in the cancer register. In 20% of the cases the tumour grade was not stated on the form. In these cases the original cytological or pathological reports were requested from the diagnosing laboratories. The cases were divided into four groups according to tumour grade: well differentiated (G1), moderately differentiated (G2), poorly differentiated (G3), and a group with unknown morphology. In 300 cases it was impossible from the original reports to classify the cases as belonging to one of the three mentioned subgroups. Most of these cases were borderline cases between the subgroups, e.g. between well and moderately differentiated tumours, or between moderately and poorly differentiated tumours. In these cases the original cytological or histological material was reviewed (by T Å and A B respectively). After review these cases were classified as follows; 43 as well differentiated, 106 as moderately differentiated, 62 as poorly differentiated whereas in 13 cases no cancer was found. In 76 cases no material was available for review. These cases were classified as belonging to the group with an unknown grade. In addition a morphologic review was performed in a randomly selected sample (140 cases) constituting 5% of the material, in order to elucidate the consistency of the diagnostics. This review was made without knowledge of the original morphology. The concordance rates are shown in Table 1. In 24 of these 140 cases no review could be carried out since the original specimens were not available.

Results

Table 2 shows basic data for the 2 618 studied cases. The mean age did not change over time. The proportion of cases microscopically verified by cytology alone increased whereas the proportion of histopathologically verified cases decreased during the period studied (Table 2). The tumour grade distribution of the 71 cases diagnosed at autopsy differed from the total material, with 44% G1-tumours in the autopsy series vs. 29% in the total material.

In a sample of 100 cases from 1974 only 14 were histologically diagnosed by transurethral resection. In 1974 the predominant diagnostic procedures were coarse needle biopsy and transvesical enucleation. This observation is in contrast to the findings from 1986–1987 when about 95% of the histologic diagnoses were based on transurethral resections. From these figures it can be estimated that approximately 100–150 more cases of prostate cancer each year were diagnosed incidentally by transurethral resections in 1986–1987 than in 1974–1975.

The age-adjusted incidence increased by 35% from 1970 to 1987 whereas the mortality remained almost constant (Fig. 1). The number of G1 and G2 tumours increased

Table 1

Concordance rates from the 'blind' review of the 5% randomly selected cases with prostate cancer. Number of diagnoses on review/number of original diagnoses in parentheses

Subgroup	1974/75	1980/81	1986/87	Total
Well differentiated	0.77 (10/13)	1.00 (4/4)	0.86 (19/21)	0.84 (32/38)
Moderately differentiated	0.78 (7/9)	0.73 (16/22)	0.64 (16/25)	0.70 (39/56)
Poorly differentiated	0.67 (6/9)	0.50 (3/6)	0.86 (6/7)	0.68 (15/22)
Total	0.74 (23/31)	0.72 (23/32)	0.75 (40/53)	0.74 (86/116)

Table 2

Basic data from the 2 618 analysed cases with postate cancer

	74/75	80/81	86/87	Total
No of cases	685	852	1 081	2 618
Range age (years)	52–95	51–97	47–94	47–97
Mean age (years)	73.4	73.9	73.9	73.7
Cytological verification	275 (40.1%)	373 (43.7%)	665 (61.5%)	1313 (50.1%)
Pathologic verification	345 (50.4%)	460 (54.0%)	384 (35.5%)	1189 (45.4%)
No morphology	65 (9.4%)	19 (2.2%)	32 (3.0%)	116 (4.4%)

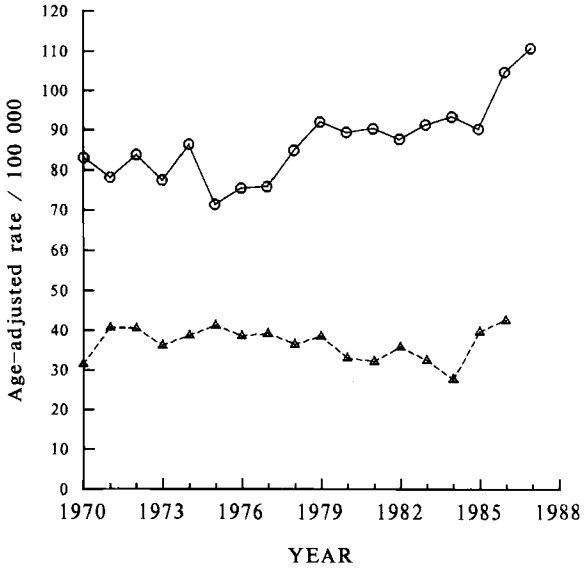

Fig. 1. Age-adjusted incidence and mortality rates of prostate cancer in northern Sweden between 1970–1987. —○— = Incidence; --△-- = Mortality.

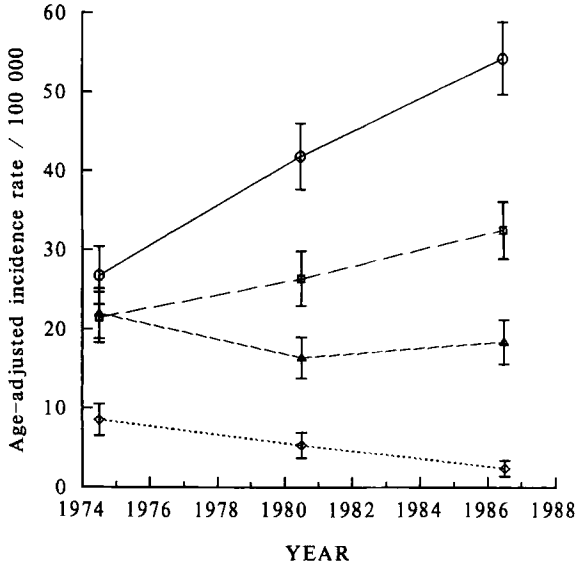

Fig. 2. Age-adjusted incidence rates for different tumour grades of prostate cancer in the three periods studied. The rates are presented with 95% confidence limits. □ = Well differentiated (G1); ○ = Moderately differentiated (G2); △ = Poorly differentiated (G3); ◇ = Others.

significantly from 1974–1975 to 1986–1987, whereas the number of G3 tumours was stable (Table 3). The 'unknown grade' group (147 cases) mainly contained cases in which the morphologic material was missing or the diagnosis was based on clinical records only. The incidence rates for G1 and G2 tumours increased while the rates for G3 tumours remained constant or even decreased (Fig. 2).

The relative survival rate (RSR) increased significantly during the studied period ($p = 0.005$, Fig. 3). The 5-year RSR was 0.61 for 1974–1975, 0.65 for 1980–1981 and 0.70 for 1986–1987. When analysing RSR within each subgroup with regard to degree of differentiation (Fig. 4a–c) there were no significant changes over time, except for the G1 tumours where some improvement of RSR was observed between 1980–1981 and 1986–1987 ($p = 0.001$). After adjustment for tumour grade the increase in relative survival, decreased (Fig. 2); and the 5-year RSR was 0.61, 0.61 and 0.66 for the three studied periods respectively (Fig. 5).

Table 3

Number of cases in each tumour grade in different time periods

	74/75	80/81	86/87	Total
G1	188	251	327	766
G2	234	399	543	1 176
G3	190	153	186	529
Unknown grade	73	49	25	147
Total	685	852	1 081	2 618

Discussion

As expected we found an increasing incidence and a stable mortality in PC in our region (Fig. 1). Similar observations have been reported also from the United States (2). Our main finding was the significantly increased incidence of G1 and G2 tumour from 1974–1975 to 1986–1987 and the unchanged incidence of G3 tumours. This finding could explain the diverging trends of incidence and

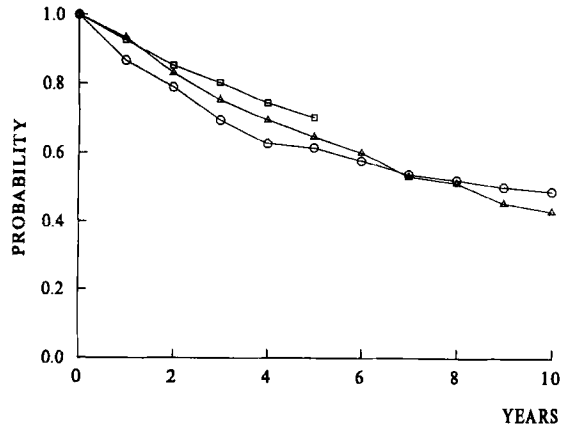

Fig. 3. Relative survival rates (RSR) of all patients with prostate cancer during the period studied. ○ = 1974/75; △ = 1980/81; □ = 1986/87; p = 0.005 at 5 years.

mortality, since the G1 and G2 tumours are often non-fatal (Fig. 4a and b) and do not contribute to the total mortality as much as G3 tumours.

The most plausible explanations for the increase of G1 and G2 tumours are a more frequent use of transurethral resection for postrate hyperplasia and of transrectal fine-needle biopsies (11). From autopsy studies it is well known that the prevalence of PC is very high, particularly in the elderly male population (12, 13). Autopsy-based prevalence rates of 20–30% at 60 years and 50–70% in males over the age of 80 have been reported. It is also obvious that the probability of incidental detection is much higher for indolent, slowly growing tumours (G1 + G2) than for more agressive, fast-growing ones (G3). Thus, in a population with low diagnostic intensity G1 and G2 tumours will often be undetected whereas G3 tumours tend to disclose themselves spontaneously by producing symptoms. This was probably the case during the 1970's and earlier in our region. Another striking trend was the doubling of the number of cases diagnosed with cytology after fine-needle aspiration biopsy. This procedure was probably used with increasing frequency in patients with asymptomatic and accidentally discovered prostatic tumours.

Another confounding factor could be that systematic changes took place over time in the morphological interpretations of the specimens, favouring a diagnosis of G1 and particularly G2 tumours over G3 lesions. In the reevaluation of 5% of all cases there was an overall concordance rate of 74% between the reviewed and the original morphology in the total material (Table 1). Due to the small number of cases in each subgroup, when the material was divided into time periods and grades, we were unable to statistically verify whether or not there had been a change over time in the morphological interpretation. However, such a change alone cannot explain the different trends in the incidence of tumours with different grade. Another reason for a rising incidence may be the increased

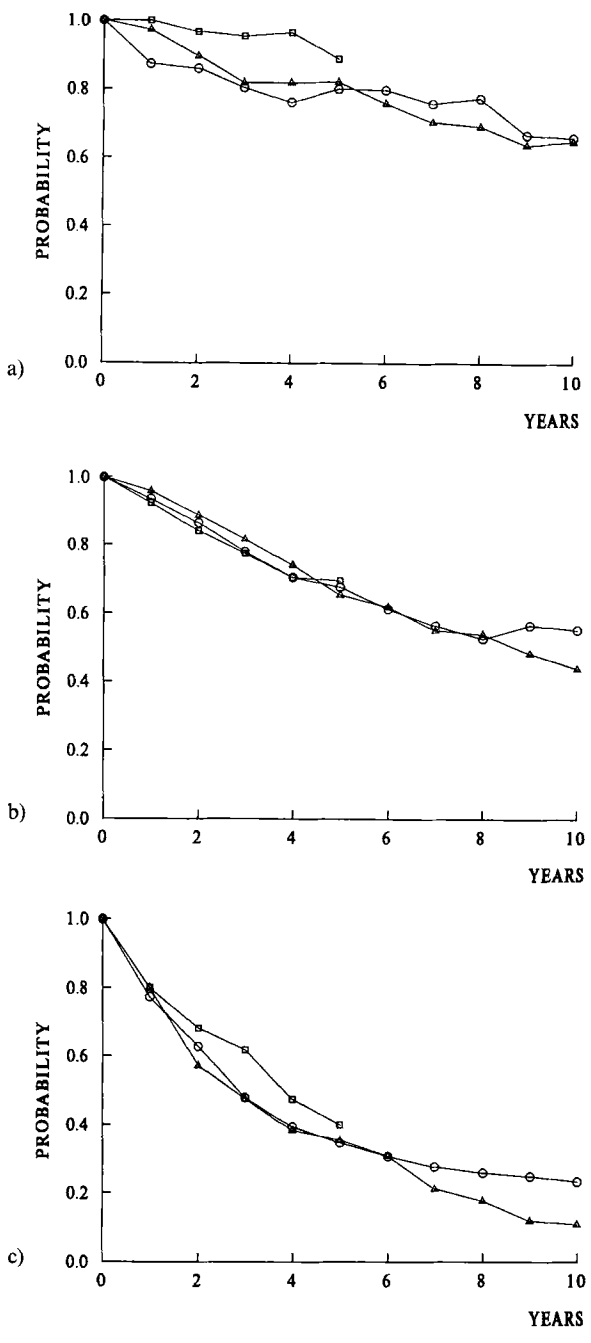

Fig. 4. Relative survival rates (RSR) for the three different tumour grades of prostate cancer. ○ = 1974/75; △ = 1980/81; □ = 1986/87; a) Well-differentiated tumours (G1) p = 0.001 at 5 years; b) Moderately differentiated tumours (G2) p = 0.08 at 5 years; c) Poorly differential tumours (G3) p = 0.31 at 5 years.

occurrence of risk factors for the development of the disease in the population. If this explanation had been a major factor in the present material, one would, however, have expected a rise in incidence of tumours in all three grades.

The overall relative survival improved significantly in our material from 1974–1975 to 1986–1987 (Fig. 3). After

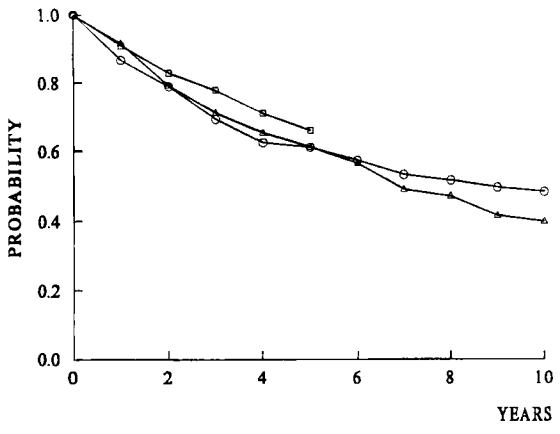

Fig. 5. Relative survival rates (RSR) for all patients during the period studied stratified for tumour grade. The grade distribution of 1974/75 is used as reference. ○ = 1974/75; △ = 1980/81; □ = 1986/87.

adjustment for tumour grade this improvement in RSR decreased considerably (Fig. 5). When RSR was estimated for each tumour grade, the survival was very similar over time for G2 and G3 tumours (Fig. 4b and c). Only RSR for G1-tumours increased significantly (Fig. 4a) and one explanation might be an increasing tendency to report borderline tumours to the cancer register. The overall improvement of surval was thus mainly due to increasing detection of non-fatal lesions rather than to improved treatment.

There are many difficulties connected with the interpretation of trends in incidence, survival and mortality in PC. Changes in trends are probably caused by a combination of the factors described above. However, in our opinion one major reason for the increasing incidence is an increased detection of non-fatal, low grade (G1 + G2) tumours. Our analysis does not support the opinion that early detection of PC, for instance by general screening, could essentially reduce the mortality of this disease (15, 16).

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