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Background: The incidence of prostate cancer has increased during the past 30 years but has been paralleled by increases in survival rates from this disease, despite the absence of documented major improvement in curative treatment. Since a high prevalence of microscopic prostate cancer has been observed in autopsied men and because many prostate cancers may never surface clinically, increased diagnostic activities might have led to increased detection of less aggressive tumors. Purpose: This study was conducted to elucidate whether the trends in prostate cancer incidence and patient survival may be due to increasing diagnoses of nonlethal tumors. Methods: We analyzed a population-based cohort comprising all cases of prostate cancer (n = 80,901) detected in Sweden during the period of 1960 through 1988. Five hundred eighteen patients (0.64% of the total number) who could not be followed because of emigration or an incomplete national registration number were excluded. Observed and relative survival rates were calculated for the entire cohort of 80,383 assessable patients per 5-year age group in 5-year periods of diagnosis and according to diagnostic method and were compared between geographic areas with differences in incidence rates. To estimate the independent effects of these determinants, multivariate analyses were performed. Results: For the 80,383 patients with complete follow-up, the 10- and 20-year observed survival rates were 17.5% (95% confidence interval [CI] = 17.2%-17.9%) and 3.5% (95% CI = 3.2%-3.7%), and the relative survival rates were 41.1% (95% CI = 40.3%-41.9%) and 28.6% (95% CI = 26.5%-30.1%), respectively. Relative survival rates improved markedly over time; 10-year relative survival rates increased from 29% (95% CI = 27%-31%) among case patients diagnosed in 1960 through 1964 to 45% (95% CI = 43%-46%) among those diagnosed in 1975 through 1979. Relative survival rates leveled off after about 18 years at 18% (95% CI = 15%-20%) among patients diagnosed in 1960 through 1964 and at 31% (95% CI = 28%-34%) among those diagnosed in 1970 through 1974. An even more favorable outlook was observed in those case patients diagnosed later. In areas with a high or low incidence of prostate cancer, the 10-year relative survival rates were 45% (95% CI = 44%-47%) and 36% (95% CI = 34%-38%), respectively. In the early 1960s, the calculated loss of life expectancy after diagnosis varied from about 68% (95% CI = 61%-75%) of the expected length of life in the youngest age group to about 48% (95% CI = 46%-50%) in the oldest age group. From 1960 through 1964 to 1985 through 1988, the loss of life expectancy decreased by more than 50% in all age groups. The differences in relative survival rates between age groups were small, with a gradual decrease in age groups more than 60-64 years of age. Conclusions: Most of the great temporal improvement and geographic variation in survival rates are quantitatively consistent, with likely increases in the rate of detection of nonlethal tumors. Implications: The increase in relative survival rates must be taken into consideration when evaluating the outcome of treatment of prostate cancer, since nonrandomized comparisons may be confounded by time trends. Diagnosis of nonlethal tumors raises concerns because the individual would suffer from the psychologic burden of a cancer diagnosis without any therapeutic benefit. [J Natl Cancer Inst 1996;88:1216-21]
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of cases diagnosed cytologically in-

declined and reached less than 5% in 1975. The

owing three groups: 1) cytologic diagnosis, 2) biop-

in the early 1960s, about 40% of the diagnoses were

nosis by fine-needle transrectal aspiration biopsy of

a traditional biopsy (23) and soon became the stand-

d diagnostic tool; large-needle core biopsy almost

went out of practice. A new era of core-verified

 biopsy began in the 1980s, when transrectal,

ultrasound-guided core biopsy was introduced. In

the early 1960s, transvesically enucleated glands

made up most of the prostate cancer tissue surgical-

ly obtained from patients. Transurethral resection

of prostate (TURP) hyperplasia was introduced in the

1960s and gradually replaced transvesical enuclea-

tion until the latter part of the 1970s as the standard

treatment for benign hyperplasia of the prostate.

Through increasing use of TURP in the succeeding

ears, a growing number of cases of nonclinical

tumors were included in the group of biopsy-

verified cases.

In our cohort, about half of the cases of prostate

cancer from the 1960s were diagnosed by his-

topathologic examination of surgical or biopsy

material. Later, these methods formed the basis

of diagnosis for roughly 40%-45% of the patients.

In the early 1960s, about 40% of the diagnoses were

made by clinical examination only, x ray, or gross

examination at surgery, but this figure gradually

decreased and reached less than 5% in 1975. The

proportion of cases diagnosed cytologically in-

creased from 15% in 1960 to 33% in 1970 and 60%

in 1975, after which only slight changes were seen.

Diagnostic methods were classified into the fol-

lowing three groups: 1) cytologic diagnosis, 2) biop-

sy diagnosis (including different types of histologic

examinations of surgical or biopsy material; in the

registry files, TURP-verified cases cannot be sepa-

rated from other biopsy-verified cases), and 3) cases

not verified histologically (clinical diagnosis only, x-ray diagnosis, and gross examination at surgery). The proportion of all prostate cancers detected first at autopsy was 9.4% in 1977 (the first year when this information was published); it decreased to 7.6% in 1981 and to 4.0% in 1988 (24).

Incidence Data

In some of Sweden's 25 counties, the incidence rates differ by more than ±15% from the national average (25). Furthermore, the three largest cities, Stockholm, Gothenburg, and Malmö, have higher incidence rates than their respective surrounding counties. These differences might reflect a geographic variation in diagnostic intensity rather than a true variation in incidence. If this assumption is true, we should expect a more favorable prognosis in high-incidence areas, because of a larger proportion of relatively benign lesions, than in low-incidence areas. On the basis of a priori decisions, the 25 counties were grouped according to their incidence rates into four categories that corresponded approx-

mately to the lowest, the two middle, and the

highest quartile of incidence during the period 1959 through 1960 (25). Thus, we classified the study subjects as follows: 1) men from high-incidence areas (>105% of the average), 2) men from low-in-

cidence areas (<85% of the average), and 3) men from intermediate-incidence areas. Corresponding data showing mortality rates by county are not avail-

able.

Statistical Methods

Observed and relative survival rates were

alyzed in the entire cohort per 5-year age groups in

5-year periods of diagnosis according to diagnostic

test method and in geographic areas with differences

in incidence rates. Observed survival rates were cal-

culated according to the actuarial (life-table) method

(26). Relative survival rates were calculated as the

ratio of observed to expected survival (27,28), the

latter based on individuals in the general population

corresponding to the cohort with respect to 5-year

age group and calendar year of observation (29). In

addition (in accordance with the actuarial method),

the expectation (mean length) of life in different

periods of diagnosis, stratified by age group, was

calculated.

To estimate the independent effects of age, diagnos-

tic period, diagnostic method, risk area, and year of

diagnosis, we performed a multivariate analysis. In

this analysis, grouped annual data were used; the

analysis was based on a generalization of the propor-

tional hazards model, in which the prostate cancer-

specific hazard rate was assumed to be additive to

the hazard rate in the general population (30,31). This model was formulated as a generalized linear model and estimates were obtained by the maximum likelihood method using the Generated Linear Incidence Model (GLIM) (30). Age at diag-

nosis was included in 10-year intervals (40-49, 50-

59, 60-69, 70-79, and 280 years), and the calendar

dates of diagnosis were divided into five categories


through 1974, 1975 through 1979, and 1980 through

1984).

In addition to models in which main effects were

analyzed, models with interaction terms were also

estimated. The estimated models were compared

with respect to deviance, which describes the fit of

the model. A deviance of the same order as the

degrees of freedom is normally taken as an indica-

tion of a reasonable fit. However, in applications

with large numbers in each cell, the variability is

often greater than indicated by the Poisson or bino-

mial theory. We used the difference in deviance not

for application of rigid statistical tests but, rather, in

combination with the pattern and size of the

parameter estimates, as an indicator of the quality of

the different models. The results are given as rela-

tive hazards of dying of prostate cancer, with 95% confidence intervals (CIs). Although the actual over-

dispersion was rather moderate, we adjusted the

standard errors for overdispersion.

Results

Overall Results

Among the 80,383 patients included in the

survival analysis, the distribution of age at diagnosis

remained fairly stable during the 29 years of inves-

tigation. The mean age at diagnosis was 73.1 years;

only 14.8% were younger than 56 years. In the entire

cohort, the observed 5-, 10-, and 20-year survival rates (with 95% CIs) were 40.0% (39.6%-40.4%), 17.5% (17.2%-17.9%), and 3.5% (3.2%-3.7%), respectively, while the relative survival rates were 58.5% (57.9%-59.0%), 41.1% (40.3%-41.9%), and 28.6% (26.5%-30.1%), respectively. Relative survival decreased rapidly during the first 5 years after diagnosis, then more slowly with no further notable decrease after about 20 years.

Temporal Trends

The 5-year relative survival rates in-

creased from 45% in 1960 through 1964 to 63% in 1980 through 1984 (Table 1). The 10-year relative survival rate in-

creased from 29% in 1960 through 1964 to 45% in 1975 through 1979 (Table 1). The improvement trend in 5- and 10-year relative survival rates could be observed in all four age groups. An approximately 1% improvement in relative survival per year was also discernible in 15-year rela-

tive survival rates during the diagnostic periods of 1960 through 1964, 1965 through 1969, and 1970 through 1975 (data not shown). During follow-up beyond 10 years, a continuing decrease in relative survival rates was seen; after 18
Table 1. Relative 5- and 10-year survival (RS) with 95% confidence intervals (CIs) for the 80,383 assessable case patients by age groups and 5-year calendar periods of diagnosis

<table>
<thead>
<tr>
<th>Age at diagnosis, y</th>
<th>1960 through 1964 RS (95% CI)</th>
<th>1965 through 1969 RS (95% CI)</th>
<th>1970 through 1974 RS (95% CI)</th>
<th>1975 through 1979 RS (95% CI)</th>
<th>1980 through 1984 RS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-54</td>
<td>42 (33-51)</td>
<td>50 (42-57)</td>
<td>59 (52-65)</td>
<td>62 (55-69)</td>
<td>50 (42-57)</td>
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<tr>
<td>55-64</td>
<td>52 (48-55)</td>
<td>58 (55-61)</td>
<td>62 (60-65)</td>
<td>65 (63-67)</td>
<td>66 (63-68)</td>
</tr>
<tr>
<td>65-74</td>
<td>46 (44-48)</td>
<td>55 (53-57)</td>
<td>60 (58-62)</td>
<td>63 (61-64)</td>
<td>65 (63-66)</td>
</tr>
<tr>
<td>75-84</td>
<td>42 (39-45)</td>
<td>48 (46-51)</td>
<td>49 (47-51)</td>
<td>56 (54-58)</td>
<td>62 (59-64)</td>
</tr>
<tr>
<td>All ages</td>
<td>45 (44-47)</td>
<td>53 (51-54)</td>
<td>56 (55-58)</td>
<td>60 (59-62)</td>
<td>63 (62-65)</td>
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<td>1960-64</td>
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<td>1965-69</td>
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<td>1975-79</td>
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<tr>
<td>1980-84</td>
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The observed average remaining length of life after diagnosis of prostate cancer varied from 7.8 years in the youngest patients (45-54 years old at diagnosis) to 3.3 years in the oldest (75-84 years old at diagnosis) in the early 1960s. This corresponds to a loss in remaining life expectancy of 68% (95% CI = 61%-75%) and 48% (95% CI = 46%-50%), respectively. In 1980-1984 the loss of life years had diminished to 58% (95% CI = 49%-68%) of that expected in patients 45-54 years old at diagnosis.
Multivariate Analyses

To assess the independent effects of the different determinants of prognosis, multivariate models were fitted. Each of the study variables, especially diagnostic method, improved the model fit, as did an interaction term between period of diagnosis and diagnostic method, which indicates that the period effects differ among diagnostic categories. During the first 5-year period of follow-up, the deviance in the basic model with all main effects was 2011 (on 1015 df). Inclusion of interaction effects reduced the deviance further.

The estimation of relative hazards during the first and second 5-year periods of follow-up shows statistically significant effects in all four groups of variables (Table 2, A). We found a successive improvement by period of diagnosis, with an approximately 30% lower relative hazard in 1980 through 1984 compared with 1960 through 1964. The effect of age was consistent with the pattern displayed in Fig. 2, with the best prognosis in the men 60-69 years old. The differences by age were somewhat less pronounced, however, with longer follow-up. Patients from high-incidence areas showed a 21%-24% lower relative hazard than those diagnosed in low-incidence areas. Within 5 years, patients diagnosed by biopsy had a better prognosis than those diagnosed by cytology, while those diagnosed by other methods had the poorest prognosis.

Finally, we explored the interaction between period of diagnosis and diagnostic method. Since cases diagnosed by methods other than cytology and biopsy most often are detected at an advanced stage, we devoted our main interest to the biopsy.
sy and cytology category (Table 2, B). The period of diagnosis had a marked effect in the biopsy group but not in the cytology group. Differences in relative hazards by age group were noted in the biopsy-diagnosed men and were even more marked in the cytology group. In both diagnostic categories, men aged 60-69 years had the lowest relative hazards. In both diagnostic categories, men from high-incidence areas had the best prognosis.

Discussion

Overall, the relative survival declined rapidly during the first 5 years of follow-up and improved markedly from 1960 through 1964 to 1985 through 1988; the loss of life expectancy decreased by more than 50%. The differences in relative survival among age groups were small, with a gradual decrease in age groups above 60-64 years. Relative survival rates were significantly higher in patients diagnosed by cytology or biopsy than in those diagnosed by clinical examination alone, x-ray, or gross examination at surgery. Furthermore, the patients from areas with a high incidence rate of prostate cancer showed higher relative survival rates than those from low-incidence areas.

Because of its large size, our study provides precise estimates of survival. Any bias is unlikely, since the overall cancer reporting is more than 96% complete (27) and the loss to follow-up minimal. Provided that the only difference in death rate between the cohort with prostate cancer and the general population is due to prostate cancer, the relative survival rate should describe the survival from prostate cancer when the effects of other causes of death have been eliminated (30). This assumption is reasonable because there are no established constitutional or lifestyle factors related to longevity that appear to differ appreciably between patients with prostate cancer and the male population at large (32). For example, recent Swedish studies suggest that neither nutritional factors (33) nor smoking (34) are associated with prostate cancer risk.

The predominant strategy in localized prostate cancer in Sweden throughout the investigation period was watchful waiting or palliative hormonal therapy, and we assume that only a small number of patients underwent treatment with the intention to cure. Less than 150 radical prostatectomies were performed yearly during the late 1980s (35). Palliative hormonal treatment has not been shown to extend the life of patients with prostate cancer (36). The observed increase in long-term relative survival rates, therefore, cannot be explained by more effective treatment or by changes in diagnostic methods (Table 2, B). A likely reason is increased diagnostic activity. Earlier diagnosis may lead to apparently longer survival times (lead-time bias), even in cases where the natural history is, in fact, not improved by early detection. However, lead-time bias alone probably could not result in more than a marginal increase in long-term relative survival.

Information on tumor grade or stage is not available in the Cancer Registry. However, among 2618 patients diagnosed in northern Sweden during the 1970s and the 1980s (a component of our study cohort), relative survival rates up to 10 years were calculated for each tumor grade in the three periods as follows: 1974 through 1975, 1980 through 1981, and 1986 through 1987 (37). The number of grade 1 and 2 tumors increased by 74% and 132%, respectively, but the number of grade 3 tumors remained stable during these 12 years. No significant increase in relative survival rate was observed after stratification for grade, which indicates that improved treatment cannot account for the trend in overall survival. Information on tumor stage, had it been available, would probably have changed in accuracy during the period of study. Most likely, more careful diagnostic work-up and improved diagnostic techniques would have produced spurious increases in stage-specific survival because of stage migration (38). Moreover, under our hypothesis, stage of disease is an intervening rather than a confounding variable. Hence, adjustment for stage would be inappropriate in our analyses of trends in overall survival rates (39).

We tested the hypothesis, that over-diagnosis of nonlethal tumors accounts for the trend in survival, by calculating the number of added nonlethal cases needed for the observed improvement in relative survival. We assumed that the patients diagnosed in 1980 through 1984 were of two categories, namely, those with the same 5-year relative survival rates as patients diagnosed in 1960 through 1964 and those with no excess death rate, i.e., a relative survival rate of 100%. To reach the 5-year relative survival observed in the cases diagnosed in 1980 through 1984, the latter category would have to comprise 33% (n = 5857) of all patients. Since there was no known change in the tumor biology of prostate cancer during the investigation period, this would imply that at least one third of all patients diagnosed in 1980 through 1984 would represent overdiagnosis of nonlethal tumors.

One important reason for the increasing detection rate of prostate cancer is the practice of TURP for presumed benign hyperplasia. In Sweden, the yearly number of TURP procedures increased from approximately 1500 in 1972 to approximately 11,000 in the late 1980s. Significant correlations were found in Canada between the rates of performance of TURP procedures and both the national and provincial incidence rates of prostate cancer (7). In Sweden, between 1958 and 1971, the incidence rate doubled while the mortality rate increased only marginally. A positive correlation was found between the incidence rate and the level of development of local medical services (40). Our study suggests that biopsy-verified tumors became diluted by an increasing proportion of nonlethal cancers, since the period effect for biopsy-verified tumors is more pronounced than in cancers verified by cytology (Table 2, B).

Another likely reason for an increasing detection rate of subclinical cancers is the improved access to health care, with more frequent routine digital rectal examinations. The health care system developed considerably in Sweden during the three decades of our investigation. The findings of increased relative survival rates and lower relative risks in patients from high-incidence areas compared with those from low-incidence areas support the view that increased diagnostic activity resulted in detection of a larger number of early stage and/or nonactive carcinomas.

Conflicting findings have been reported concerning the influence of age at diagnosis on survival (41). Some investigators (42,43) found a poorer prognosis.
in younger men, and others found a poorer prognosis in elderly patients (8,17,44,45). Similar to an earlier Swedish study (46), our data indicate that the association with age at diagnosis is weak and nonlinear.

Some survival analyses on comparatively small prostate cancer cohorts have been published from other Scandinavian countries. In Finland (18), Denmark (8), and Norway (17), the 5-year relative survival rates increased significantly during the last 30 years. The Danish data show a progressive increase in relative survival from the 1940s to the 1970s, but in the same time period, a somewhat smaller increase in relative survival rates than in the other Scandinavian countries. The positive survival trends during the 1960s and the 1970s in these studies fit well with our findings.

In conclusion, most of the major improvement in survival rates is probably not a result of improved treatment but of increased detection of nonlethal tumors and lead-time bias. The increase in relative survival must be taken into consideration when treatment of prostate cancer is evaluated, since nonrandomized comparisons may be confounded by time trends. Increased diagnostic intensity might lead to curative treatment in some patients with aggressive disease for the reason that they are diagnosed at an early stage. However, detection of nonlethal tumors may be harmful rather than beneficial to the individual, thus raising concerns that need to be discussed openly.

References


Notes

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