Concordance of Survival in Family Members With Prostate Cancer

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ABSTRACT

Purpose
Several earlier studies have assessed survival in prostate cancer based on familial risk of this disease. As a novel concept, we posit that factors governing survival in prostate cancer are likely to be different from those governing risk of prostate cancer. To prove this, we searched for familial clustering of survival (ie, concordance of survival among family members).

Patients and Methods
We used the nationwide Swedish Family-Cancer Database to estimate hazard rates (HRs) for cause-specific and overall survival in invasive prostate cancer. HRs show the probability of death in the study group compared with the reference group. The study covered 610 sons of affected fathers with median follow-up times for survival ranging from 34 to 76 months.

Results
When the survival in sons was analyzed according to the fathers’ length of survival, there was a concordance of prognosis; the HR was 0.62 for sons whose fathers had survived longer than 59 months, compared with sons whose fathers had survived fewer than 24 months (P for trend, .02). On a continuous scale, the sons’ survival increased almost linearly with the fathers’ survival time. When the analysis was reversed and HRs were derived for fathers, the concordance of good and poor survival remained.

Conclusion
The results are consistent in showing that both good and poor survival in prostate cancer aggregate in families. Genetic factors are likely to contribute to the results, which provide the first challenging population-level evidence on heritability in prognosis of prostate cancer.

INTRODUCTION

The incidence of prostate cancer has continuously increased in the Western countries, most recently probably because of the wide application of prostate-specific antigen (PSA) testing.1 However, mortality from prostate cancer has remained stable, indicating improving survival, which may largely be ascribed to lead-time bias (earlier diagnosis) and case-mix bias (larger fraction of nonfatal tumors).2,3 As a result, 5-year relative survival in prostate cancer is better than 75% in Sweden.4 Although family history is one of the best known risk factors for prostate cancer, its possible influence on prostate cancer survival is not well established, despite numerous studies. Even though some of the earlier studies suggested that a familial disease may have a more aggressive course, many newer studies have suggested no difference between the sporadic and familial disease.6-15 To date, the data suggest that the survival of patients with a family history is not essentially different from that of patients with sporadic prostate cancer.

PSA testing has been suggested to be one of the reasons for the inconsistent family history results on the prognosis of prostate cancer.6 However, we are concerned that attempts to correlate survival with measures of cancer risk (family history) may not be meaningful, because survival is dependent on tumor progression and metastasis, whereas risk (tumorigenicity) is related to defects in cell cycle control and DNA integrity.16-20 A proper familial measure for survival should be survival itself (ie, familiality in survival among family members). Accordingly, favorable survival should be shared by family members, for which supporting data have recently been published on breast cancer from Sweden.21,22 We propose that survival in prostate cancer has a heritable component and we want to test this here using data from the nationwide Swedish Family-Cancer Database. Recent data from Iceland showed that carriers of the BRCA2 founder mutation 999del5...
had worse survival than men without this mutation.23 Even other identified genetic factors have been suggested to be related to the prognosis of prostate cancer, but the role for environmental factors, such as diet, has not been established.24,25 However, obesity may be associated with poorer prognostic markers and early biochemical relapse in African-American men.26

**PATIENTS AND METHODS**

The Family-Cancer Database was created by linking information from the multigeneration register, national censuses, Swedish Cancer Registry, and death notifications.27,28 Data on family relationships were obtained from the multigeneration register, in which children born in Sweden in 1932 and later are registered with their biologic parents as families. The database was updated in 2006 to include patients with cancer from 1958 to 2004.28 The second generation (sons) had reached an age of 72 years; the ages in the first generation (fathers) were not limited. Information retrieved from the various registers was linked at the individual level via the national 10-digit civic registration number assigned to each person in Sweden for his or her lifetime. Before inclusion in the database (MigMed2), civic registration numbers were replaced by serial numbers to ensure anonymity of all individuals. The Swedish Cancer Registry is based on compulsory reports of diagnosed cases provided by physicians (clinical report) and by pathologists or cytologists (pathology report); the coverage of the cancer registration is currently considered to be close to 100%.

Only instances classified as primary neoplasms of the prostate (International Classification of Diseases, ICD, seventh revision, code 174) were considered in this study. Analysis was done separately for prostate cancer in sons and fathers. A total of 4,663 sons were diagnosed with prostate cancer between 1990 and 1999, 610 of whom had a father affected with prostate cancer before 1990. For paternal prostate cancers, 48,461 instances were noted before 1990. Cases were defined as familial when sons were diagnosed with prostate cancer between 1990 and 1999 (609 cases because one father had two affected sons). Follow-up for survival began at diagnosis and it was terminated at death, emigration, or the closing date of the study (December 31, 2004), whichever came first. Data were retrieved also for affected brothers but only 47 affected brother pairs were diagnosed before year 2000; only two patients died of cause specific and 10 of overall causes during the follow-up period. Because of the small numbers, no conclusions can be drawn. When survival in sporadic prostate cancer was considered, the median year of diagnosis was matched with that of familial cancer.

Cox’s proportional hazards regression models were used to estimate the hazard rates (HRs) for disease-specific and overall survival associated with family history. HR indicates the relative risk of dying in the defined period compared with a reference group; when it is below 1.0, the risk is lower than in the reference group. HR was adjusted for age at diagnosis (continuous variable), period (1961 to 1979 and 1980 to 1989 in paternal prostate cancer; 1990 to 1994 and 1995-1999 in offspring prostate cancer), socioeconomic status (manual worker, blue collar, professional, and others) and diagnosis region (Stockholm-Gotland, Uppsala, southeastern region, southern region, western region and northern region).

For the analysis of disease-specific survival, deaths as a result of prostate cancer were the primary end point; deaths due to other causes were censored. For the analysis of overall survival, deaths due to any cause were the end point. The proportional hazards assumption for the covariates was tested by Schoenfeld residuals and by plotting the log of the negative log of the survival function versus the log of time; covariates were stratified in the models if they did not meet the assumption. Tests for trend were done for familial prostate cancer by treating probands’ survival time as a continuous variable in the models. We used restricted cubic spline regression with four knots to flexibly model the association between mortality in familial prostate cancer and probands’ survival time.26 All statistical analyses were performed using SAS software, version 9.1 (SAS Institute, Cary, NC).

**RESULTS**

For offspring prostate cancer, HR was 0.99 (95% CI, 0.96 to 1.02) for overall survival when diagnosis age increased by 1 year; HR was 0.56 (95% CI, 0.40 to 0.79) for overall survival when sons were diagnosed in 1995 to 1999 compared with those diagnosed in 1990 to 1994. For paternal prostate cancer, HR was 1.05 (95% CI, 1.04 to 1.06) for offspring prostate cancer, HR was 0.99 (95% CI, 0.96 to 1.02) for overall survival when diagnosis age increased by 1 year; HR was 0.56 (95% CI, 0.40 to 0.79) for overall survival when sons were diagnosed in 1990 to 1994 and 1995-1999 in offspring prostate cancer).

### Table 1. Hazard Rates for Cause-Specific and Overall Survival in Familial Prostate Cancer Divided By Probands’ Survival Time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of Patients</th>
<th>Median Year of Diagnosis</th>
<th>Median Follow-Up (months)</th>
<th>Cause-Specific Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Deaths</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Familial prostate cancer in sons diagnosed in the 1990s</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fathers’ survival time, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24</td>
<td>196</td>
<td>1997</td>
<td>73</td>
<td>52</td>
<td>26.5</td>
</tr>
<tr>
<td>24-59</td>
<td>166</td>
<td>1997</td>
<td>76</td>
<td>41</td>
<td>24.7</td>
</tr>
<tr>
<td>≥ 60</td>
<td>248</td>
<td>1997</td>
<td>75</td>
<td>43</td>
<td>17.3</td>
</tr>
<tr>
<td>P for trend test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial prostate cancer in fathers diagnosed before 1990</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sons’ survival time, months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>127</td>
<td>1977</td>
<td>34</td>
<td>87</td>
<td>68.5</td>
</tr>
<tr>
<td>≥ 60</td>
<td>482</td>
<td>1978</td>
<td>46</td>
<td>342</td>
<td>71.0</td>
</tr>
</tbody>
</table>

*NOTE. Hazard rates adjusted for age, period, region and socioeconomic status. Bold font indicates that 95% CI does not include 1.00.*
We analyzed survival after prostate cancer for sons diagnosed between 1990 and 1999 when their fathers were diagnosed before 1990 (Table 1). When survival in sons was analyzed according the fathers’ length of survival (fathers as probands; reference category fathers who survived fewer than 24 months), there was a concordance of survival: the longer the survival time of the father, the better the survival of the son (P for trend, 0.02 for cause-specific survival). In Table 1, median follow-up times for survival ranged from 70 to 76 months; 22.3% of the sons with a family history had died of prostate cancer, and the overall mortality was 29.5%. The median years of diagnosis were identical for all the categories (1997). The regression spline curve shows a successively better survival for sons of fathers with good survival; after about 90 months (7.5 years) the upper 95% CI does not include 1.00 (Fig 1).

Reversing the analysis for the same father-son pairs and deriving HRs for fathers who were diagnosed before 1990 (sons as probands) showed that HRs were significantly decreased for cause-specific (borderline significance) and overall survival if their sons had survived 60 months or longer (HRs 0.78 and 0.76, respectively), indicating correlation for survival experience (Table 1). Cause-specific mortality was 70.4% and the overall mortality was 99.3% for the familial cases. Median follow-up times ranged from 34 to 46 months, with year 1977/1978 as the median year of diagnosis.

In order to study the possible effects of unmeasured environmental factors on prostate cancer survival, we used mortality in cardiovascular diseases and diabetes as surrogates. Risk factors for these diseases, such as obesity, diet, and other lifestyle factors, could potentially affect survival in prostate cancer. Table 2 presents the distribution of associated causes of mortality in cardiovascular diseases and diabetes in patients who died of prostate cancer. In addition, it presents the distribution of deaths in cardiovascular diseases and diabetes in patients with prostate cancer who died of causes other than prostate cancer. The data are shown only for the fathers reported in Table 1 because of a small number of deaths for causes other than prostate cancer in sons. For comparison, we show data on sporadic prostate cancer, adjusted for the median year of diagnosis to be equal with the familial cases. The distribution of deaths in the prostate cancer survival classes was tested using the heterogeneity test, which would be significant if the proportions of deaths in the classes differed from each other. The tests for the proportions of cardiovascular disease and diabetes deaths in survival classes for sporadic prostate were significant. However, the proportions of deaths in the class with survival fewer than 24 months tended to be fewer than those in the class with survival longer than 60 months; the results suggest that poor survivors in prostate cancer shared risk factors for cardiovascular diseases and diabetes no more, or even less than good survivors. The heterogeneity tests for deaths in cardiovascular diseases and diabetes in survival classes for familial prostate cancer were not significant but the numbers of diabetic deaths were small. The equal distribution of cardiovascular deaths between the survival classes lends no support to differential sharing of risk factors for any survival group. Moreover, the equal proportions of cardiovascular deaths in each survival class between familial and sporadic prostate cancers provides no evidence for the aggregation of cardiovascular risk factors in familial prostate cancer or any familial survivor group.

DISCUSSION

We tested a novel concept in this article: are family members concordant for their survival experience? The results were consistently affirmative, indicating that family members shared either good or poor prognoses. The effect was strongest for cause-specific survival in sons, whose HR was 0.62 when their fathers had survived 60 months or longer (P for trend, 0.02). Following sons’ HRs for survival on a continuous scale showed an almost linear decrease in HR for sons in relation to improved survival in fathers (Fig 1). In the reverse analysis, the HR was 0.78 for fathers whose sons has survived 60 months or longer. To our knowledge, this is the first time familiality in survival in prostate cancer is being demonstrated. We believe that despite the complex study design, no identifiable source of bias can explain the results. We did not have information on tumor characteristics, but earlier studies from Sweden and many other countries have found no differences in tumor grade at diagnosis between familial and sporadic cases. Whether there are such differences has a limited relevance to the present conclusions, because the present focus was in survival within the group of familial cases, where we found concordance in survival experience between fathers and sons. Indeed, the genes that govern susceptibility to prostate cancer may be distinct from those governing progression and survival.

An access to the nationwide database confers a major advantage to this survival study because the data were available on a large population with registered family structures and medically verified cancers. However, truncations are almost inevitable in two-generation studies on national registers because the relatively good overall prognosis of prostate cancer requires a long follow-up time. Moreover, because prostate cancer is an old age disease, most sons of affected fathers were diagnosed toward the end of the study period, limiting the length of the follow-up for survival. Thus, of close to 2,500 affected son-father pairs in the database, only 610 pairs were eligible to this study; among more than 400 affected brother pairs only two prostate cancer deaths...
were recorded (see Patients and Methods). Even if the overall mortality in sons reached no more than 30%, the follow-up in fathers reached an almost 100% mortality. The many truncations of data, the increasing incidence of prostate cancer, and the improved survival among patients with prostate cancer raise analytic concerns. The survival rate in prostate cancer has almost doubled in the past 40 years in Sweden, the effect of which can be noted even in the displayed data (Table 1). However, it is unlikely that the changes in incidence and survival would have a pronounced influence on the results, because the data were adjusted for period and age, and because the median years of diagnosis were almost equal between the study groups.

The remaining question is whether the results on the familial concordance of good and poor survival relate to the effects of heritable genes that control survival through tumor progression and metastasis, or whether they relate to behavioral effects, such as active seeking of medical contacts in some families and avoidance in others. The data were adjusted for socioeconomic and regional factors, but nevertheless the effects remained. It seems unlikely that behavioral patterns would be carried on in such a consistent way to late adulthood in the next generation. Moreover, the consistent concordance of survival experience between fathers and sons, whose diagnoses were in nonoverlapping periods, separated by two decades into pre-PSA and post-PSA eras, would be difficult to explain by behavioral effects. Fathers’ behavior could not be influenced by sons’ subsequent diagnosis, whereas sons’ behavior could be influenced by fathers’ prior diagnosis. An aggressive course of disease in fathers might have been of more concern to sons than a benign course, which could have led to an earlier diagnosis and prolonged survival in sons. Stage migration has been observed in familial prostate cancer, but again the effect would be expected to be more pronounced in families with aggressive prostate cancer, opposite to these findings. Thus, these findings are more compatible with a heritable influence on survival than with a behavioral one. Hardly any environmental risk factors have been established for prostate cancer survival, with the possible exception of obesity. The results in Table 2 suggested that the observed survival differences in prostate cancer could not be explained by risk factors of cardiovascular disease or diabetes, such as obesity or dietary habits. The deaths in diabetes were few in patients with familial prostate cancer, but the equal proportions of cardiovascular deaths among good and poor survivors of familial and sporadic prostate cancer provided evidence against differential distribution of cardiovascular risk factors between the survivors. However, in order to rule out the possible contribution by behavioral and environmental factors, data on these would be needed. Also data on clinical prognostic factors, such as stage and Gleason grade, might have shed light on the observed results; unfortunately such data were not available in the database.

Most current models of metastasis view it as a gradual process whereby cells in the primary tumor acquire a metastatic potential through a number of somatic events. In this study, we examined the possible heritable contribution to survival in prostate cancer. As a novel hypothesis we posit that the survival experience is in part heritable, which has never been tested for prostate cancer in a population-level study. In agreement with the hypothesis, the recent Icelandic data showed poor survival in prostate cancer for BRCA2 mutation carriers. The obtained results showed concordance in good and poor survival, and the consistency of the findings strongly suggests a heritable causation, even though the lack of data on the clinical prognostic factors did not allow exclusion of the contributions by behavioral and other unknown factors. This study was hypothesis generating with the major limitation that the results could not be internally controlled among other types of relatives, such as siblings or second-degree relatives, which needs to be addressed in other settings. These novel observations call for intensified efforts to consider heritability as one mechanism regulating prognosis in prostate cancer.

### Table 2. No. of Deaths From Cardiovascular Diseases and Diabetes in Fathers Diagnosed With Prostate Cancer Before 1990

<table>
<thead>
<tr>
<th>Survival (months)</th>
<th>Cases of Prostate Cancer</th>
<th>Prostate Cancer Deaths</th>
<th>Other Deaths in Patients With Prostate Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total No. of Deaths</td>
<td>Cardiovascular Diseases</td>
</tr>
<tr>
<td>Sporadic cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24</td>
<td>9,927</td>
<td>6,798</td>
<td>2,240</td>
</tr>
<tr>
<td>24-59</td>
<td>7,979</td>
<td>6,203</td>
<td>1,957</td>
</tr>
<tr>
<td>≥ 60</td>
<td>13,670</td>
<td>8,309</td>
<td>3,327</td>
</tr>
<tr>
<td>P*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial cases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24</td>
<td>195</td>
<td>137</td>
<td>52</td>
</tr>
<tr>
<td>24-59</td>
<td>166</td>
<td>126</td>
<td>43</td>
</tr>
<tr>
<td>≥ 60</td>
<td>248</td>
<td>166</td>
<td>65</td>
</tr>
<tr>
<td>P*</td>
<td></td>
<td>.67</td>
<td>.41</td>
</tr>
</tbody>
</table>

NOTE. Bold font indicates statistical significance. *x2 test for heterogeneity.
References