Family History and Probability of Prostate Cancer, Differentiated by Risk Category: A Nationwide Population-Based Study

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Abstract

Background: Familial prostate cancer risk estimates are inflated by clinically insignificant low-risk cancer, diagnosed after prostate-specific antigen testing. We provide age-specific probabilities of non-low- and high-risk prostate cancer.

Methods: Fifty-one thousand, eight hundred ninety-seven brothers of 32,807 men with prostate cancer were identified in Prostate Cancer data Base Sweden (PCBaSe). Nelson-Aalen estimates with 95% confidence intervals (CIs) were calculated for cumulative, family history–stratified probabilities of any, non-low- (any of Gleason score $\geq 7$, prostate-specific antigen [PSA] $\geq 10$ ng/mL, T3-4, N1, and/or M1) and high-risk prostate cancer (Gleason score $\geq 8$ and/or T3-4 and/or PSA $\geq 20$ ng/mL and/or N1 and/or M1).

Results: The population probability of any prostate cancer was 4.8% (95% CI = 4.8% to 4.9%) at age 65 years and 12.9% (95% CI = 12.8% to 12.9%) at age 75 years, of non-low-risk prostate cancer 2.8% (95% CI = 2.7% to 2.8%) at age 65 years and 8.9% (95% CI = 8.8% to 8.9%) at age 75 years, and of high-risk prostate cancer 1.4% (95% CI = 1.3% to 1.4%) at age 65 years and 5.2% (95% CI = 5.1% to 5.2%) at age 75 years. For men with one affected brother, probabilities of any prostate cancer were 14.9% (95% CI = 14.1% to 15.8%) at age 65 years and 30.3% (95% CI = 29.3% to 31.3%) at age 75 years, of non-low-risk prostate cancer 7.3% (95% CI = 6.7% to 7.9%) at age 65 years and 18.8% (95% CI = 17.9% to 19.6%) at age 75 years, and of high-risk prostate cancer 3.0% (95% CI = 2.6% to 3.4%) at age 65 years and 8.9% (95% CI = 8.2% to 9.5%) at age 75 years. Probabilities were higher for men with a stronger family history. For example, men with two affected brothers had a 13.6% (95% CI = 9.9% to 17.6%) probability of high-risk cancer at age 75 years.

Conclusions: The age-specific probabilities of non-low- and high-risk cancer presented here are more informative than relative risks of any prostate cancer and more suitable to use for counseling men with a family history of prostate cancer.

American and European clinical guidelines recommend men with a family history of prostate cancer to obtain prostate-specific antigen (PSA) testing from age 40 to 50 years (1,2). The recommendations are based on epidemiological studies showing a two- to five-fold increased relative risk of prostate cancer for these men (3,4). However, in the present “PSA era,” familial aggregation of prostate cancer is often caused by increased diagnostic activity (PSA testing) among relatives of men with a recently diagnosed prostate cancer, rather than by shared genetic predisposition (5). As a consequence, the magnitude of the increased prostate cancer risk for men with a family history of prostate cancer is to a large extent inflated by familial aggregation of “PSA detected,” clinically insignificant, low-risk prostate cancer (5,6). The risk estimates presently used for counseling of...
Methods

The Prostate Cancer Data Base Sweden

The Prostate Cancer data Base Sweden (PCBaSe) 3.0 was created through record linkages between the National Prostate Cancer Register (NPCR) of Sweden and several other nationwide, population-based health care registers and demographic databases. The NPCR of Sweden captures 98% of the prostate cancer cases in the Swedish Cancer Registry, to which registration is mandated by law (9). PCBaSe has previously been described in detail (10). The quality and completeness of the NPCR (11), as well as of other Swedish national registers and databases, are high, and notifications are regularly reviewed by Statistics Sweden.

Information in PCBaSe on family history was obtained from the Multi-Generation Register, which is held by Statistics Sweden. The register includes family information for all individuals born in Sweden since 1932 and who were still residents in Sweden after 1961 or later. In 2007, there were about nine million index persons in the register who could be linked to their first-degree relatives (biological parents, siblings, and children). Practically all first-degree relatives alive after 1990 are registered. Figure 1 shows the selection of families for the final study cohort, which included 51 897 brothers of 32 807 men with prostate cancer. Half-brothers of index cases with a common father were included (n = 4035), whereas half-brothers with a common mother were excluded. All brothers whose father was not registered in the Swedish Cancer Registry as diagnosed with prostate cancer were included in the analysis of the effect of the father’s prostate cancer and differentiating these probabilities by the number of affected relatives, the relatives’ ages at diagnosis, and the risk category or severity of the relatives’ cancer.

Statistical Analysis

Nelson-Aalen estimates were used to calculate cumulative probabilities of prostate cancer with 95% confidence intervals (CIs) for brothers of the index cases in PCBaSe and for men in the general population, using age as time scale. The number of men at risk (the denominator) in the estimates for the general population was acquired from Statistics Sweden whereas the denominator in the estimates for the brothers of the index cases was acquired from PCBaSe. The number of prostate cancer cases observed among men at risk (the numerator) was acquired from PCBaSe. The probability of prostate cancer was calculated as 1-exp(-Nelson-Aalen estimator) (12). As there were few men at risk before age 50 years, the precision of probability estimates before that age would be low. We therefore present probabilities conditioned on no prostate cancer diagnosed before age 50 years. The brothers of the index cases were followed from the date of entry into one of the specific risk categories, as defined by the dates for new prostate cancer diagnoses in their family, to the date of their own diagnosis of prostate cancer.
emigration, or death to December 31, 2012, whichever occurred first. P values for comparisons between probabilities for men with different family histories were calculated using the Wald statistic. A P value of less than .05 was considered statistically significant, and all statistical tests were two-sided.

**Results**

For men in the general Swedish population, the probabilities of any prostate cancer were 4.8% (95% CI = 4.8% to 4.9%) at age 65 years, 12.9% (95% CI = 12.8% to 12.9%) at age 75 years, and 17.1% (95% CI = 17.0% to 17.2%) at age 80 years; the probabilities of non-low-risk prostate cancer were 2.8% (95% CI = 2.7% to 2.8%) at age 65 years, 8.9% (95% CI = 8.8% to 9.0%) at age 75 years, and 12.7% (95% CI = 12.6% to 12.8%) at age 80 years; and the probabilities of high-risk prostate cancer were 1.4% (95% CI = 1.3% to 1.4%) at age 65 years, 5.2% (95% CI = 5.1% to 5.2%) at age 75 years, and 8.2% (95% CI = 8.1% to 8.2%) at age 80 years.

The probabilities of any, non-low-risk, and high-risk prostate cancer increased with the number of affected family members and with age. The probabilities at age 65 and 75 years are shown in Table 1 and displayed graphically in Figures 2-5. For example, for men with one affected brother, the probabilities of any prostate cancer were 14.9% (95% CI = 14.1% to 15.8%) at age 65 years, 30.3% (95% CI = 29.3% to 31.3%) at age 75 years, and 36.1% (95% CI = 34.8% to 37.4%) at age 80 years; the probabilities of non-low-risk prostate cancer were 7.3% (95% CI = 6.7% to 7.9%) at age 65 years, 18.8% (95% CI = 17.9% to 19.6%) at age 75 years, and 24.2% (95% CI = 23.0% to 25.5%) at age 80 years; and the probabilities of high-risk prostate cancer were 3.0% (95% CI = 2.6% to 3.4%) at age 65 years, 8.9% (95% CI = 8.2% to 9.5%) at age 75 years, and 12.7% (95% CI = 11.5% to 13.8%) at age 80 years. Men with two brothers with prostate cancer had at age 75 years a 55.1% (95% CI = 49.8% to 59.9%) probability of any prostate cancer, a 33.2% (95% CI = 28.2% to 37.8%) probability of non-low-risk cancer, and a 13.6% (95% CI = 9.9% to 17.6%) probability of high-risk cancer.

**Table 1.** Probabilities (95% confidence intervals) of prostate cancer at age 65 and 75 years in Swedish men according to their family history of prostate cancer.

<table>
<thead>
<tr>
<th>Family history</th>
<th>Any PCa, %</th>
<th>Non-low-risk PCa, %</th>
<th>High-risk PCa, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By age 65 y</td>
<td>By age 75 y</td>
<td>By age 65 y</td>
</tr>
<tr>
<td>Population risk†</td>
<td></td>
<td></td>
<td>1.4 (1.3 to 1.4)</td>
</tr>
<tr>
<td>1 brother, any PCa</td>
<td>38 921</td>
<td>14.9 (14.1 to 15.8)</td>
<td>8.9 (8.8 to 8.9)</td>
</tr>
<tr>
<td>1 brother, any PCa</td>
<td>11 660</td>
<td>13.8 (12.5 to 15.1)</td>
<td>16.9 (15.5 to 18.2)</td>
</tr>
<tr>
<td>1 brother, any PCa</td>
<td>24 404</td>
<td>15.7 (14.5 to 16.9)</td>
<td>19.9 (18.8 to 21.0)</td>
</tr>
<tr>
<td>1 brother, any PCa</td>
<td>12 769</td>
<td>16.1 (14.5 to 17.6)</td>
<td>19.7 (18.3 to 21.1)</td>
</tr>
<tr>
<td>Father (brother) + brother PCa</td>
<td>7757</td>
<td>29.8 (27.0 to 32.5)</td>
<td>28.2 (25.8 to 30.5)</td>
</tr>
<tr>
<td>Father (brother) + brother PCa</td>
<td>38 946</td>
<td>26.5 (22.1 to 30.6)</td>
<td>26.2 (22.9 to 29.4)</td>
</tr>
<tr>
<td>Father (brother) + brother PCa</td>
<td>3 007</td>
<td>28.9 (19.3 to 37.4)</td>
<td>26.2 (22.9 to 30.1)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>11 750</td>
<td>21.0 (15.4 to 26.2)</td>
<td>24.5 (19.0 to 29.6)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>17 700</td>
<td>34.4 (19.6 to 50.7)</td>
<td>12.7 (21.5 to 33.6)</td>
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<tr>
<td>Father, any PCa</td>
<td>9 266</td>
<td>36.2 (16.1 to 51.5)</td>
<td>25.2 (15.4 to 33.9)</td>
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<tr>
<td>Father, any PCa</td>
<td>6 375</td>
<td>29.0 (25.6 to 32.3)</td>
<td>27.7 (25.1 to 30.3)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>2 579</td>
<td>26.4 (20.9 to 31.5)</td>
<td>25.6 (21.5 to 29.5)</td>
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<tr>
<td>Father, any PCa</td>
<td>3 671</td>
<td>31.1 (26.6 to 35.4)</td>
<td>29.0 (25.5 to 32.4)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>1 841</td>
<td>34.2 (27.1 to 40.6)</td>
<td>28.2 (23.3 to 32.9)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>1 183</td>
<td>29.8 (21.0 to 37.6)</td>
<td>27.5 (20.3 to 34.0)</td>
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<td>Father, any PCa</td>
<td>5 199</td>
<td>33.6 (18.8 to 45.7)</td>
<td>14.1 (5.4 to 22.1)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>6 466</td>
<td>25.1 (17.4 to 32.2)</td>
<td>16.4 (9.3 to 22.8)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>2 922</td>
<td>22.9 (9.3 to 34.7)</td>
<td>18.0 (5.5 to 28.8)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>2 343</td>
<td>34.4 (28.1 to 40.1)</td>
<td>33.2 (28.2 to 37.8)</td>
</tr>
<tr>
<td>Father, any PCa</td>
<td>7 099</td>
<td>43.9 (33.7 to 55.2)</td>
<td>39.4 (29.2 to 48.1)</td>
</tr>
</tbody>
</table>

†The risk for men with a negative family history is approximately 10% lower than the population risk.

‡The risk for men with a negative family history is approximately 10% lower than the population risk.
Most men with a family history of prostate cancer had a 30% to 60% probability of any prostate cancer at age 75 years, but around half of them were diagnosed with low-risk cancer. Their probability of high-risk prostate cancer was typically one-sixth to one-fourth of the probability of any prostate cancer (Table 1). The relative risks of familial prostate cancer decreased with age, for example, of any prostate cancer for brothers of men with prostate cancer from 3.1 (95% CI = 2.9 to 3.3) at age 65 years to 2.4 (95% CI = 2.3 to 2.4) at age 75 years and to 2.1 (95% CI = 2.0 to 2.2) age 80 years.

For men with a father diagnosed before age 75 years, the probabilities of non-low-risk and of high-risk cancer at age 65 years were higher than for men with a father diagnosed after age 75 years (P = .005 and P = .05) (Table 1 and Figure 4). We did not analyze the effect of the age at diagnosis of an affected brother because the age at diagnosis for affected brothers covaries as they are likely to be of similar age. For example, brothers of men diagnosed in their fifties are younger and therefore at risk of being diagnosed in their fifties or sixties whereas most brothers of men diagnosed with prostate cancer at age 75 years are in their seventies (had these brothers been diagnosed in their fifties or sixties, they would have been the index case the family). Neither the brothers’ nor the fathers’ cancer’s risk category statistically significantly affected the probability of any, non-low- or high-risk disease (Table 1).

**Discussion**

We present, for the first time, age-specific probabilities of non-low- and high-risk prostate cancer for men with a family history of prostate cancer. Most of these men had a 30% to 60%
probability of any prostate cancer at age 75 years, but around half of the diagnosed cancers were in the low-risk category and of little clinical significance. The men’s probability of high-risk prostate cancer was much lower, typically one-sixth to one-fourth of the probability of any prostate cancer. For example, men with two brothers with prostate cancer had at age 75 years a 55.1% probability of any prostate cancer, a 33.2% probability of non-low-risk cancer, and a 14.6% probability of high-risk cancer. Clearly, the probabilities of non-low-risk and, in particular, high-risk cancer are highly relevant when counseling men with familial prostate cancer. We suggest that these probabilities are included in future clinical guidelines.

In agreement with the results from our previous studies on familial prostate cancer (5,6), the present study indicates that PSA testing leads to an “inflation” of familial prostate cancer risks. Only 2.0% of men in the general population were diagnosed with low-risk cancer at age 65 years, compared with 7.6% of men with one affected brother and 20.1% of men with two affected brothers. These absolute differences are much larger than the corresponding differences for high-risk cancer. Because low-risk prostate cancer almost always is diagnosed after PSA testing, our results strongly suggest that PSA testing is more common among men with than in men without a family history of prostate cancer.

Almost all previous studies of familial prostate cancer have reported relative risk estimates (relative risks, rate ratios, hazard ratios, or standard incidence ratios). The notion of a relative risk may be difficult to grasp, and absolute risks are therefore recommended for clinical counseling (7,8). The age-specific probabilities provided by our study are in essence absolute risks and will be useful for clinicians who discuss the risk of familial prostate cancer with their patients. Experts in risk communication recommend visualization of absolute risks in the form of pictograms (7,8). We therefore provide two pairs of pictograms as examples of how our results may be presented to laypeople (Figure 5).

The probability of high-risk prostate cancer was affected by the number of affected family members and by the severity of the prostate cancer diagnosed in a father, but not by the brother’s cancer’s risk category: The probability of a future high-risk prostate cancer for brothers of men with a low-risk cancer was only slightly lower than for brothers of men with a high-risk cancer. This is a clinically important finding; brothers of men diagnosed with a low-risk prostate cancer should not be recommended against PSA testing just because their brother’s cancer might have been considered clinically insignificant.

We have previously shown that brothers of men with Gleason score 8-10 cancer are at a particularly high relative risk of cancer with the same Gleason score (6). The proportion of brother pairs concordant for Gleason score 8-10 cancer in that study was, however, small. This means that the effect size of Gleason score 8-10 cancer heritability on the absolute probability reported in the present study is small and compatible with the only slightly higher probability of high-risk cancer among brothers of men with high-risk cancer.

Our study shows that relative risks of familial prostate cancer decrease with age. The relative risk of any prostate cancer for brothers of men with prostate cancer was 3.1 at age 65 years, which is exactly the same as reported in a meta-analysis of 16 studies (3), but decreased to 2.4 at age 75 years and to 2.1 at age 80 years. This is in agreement with a previous study that reported absolute risks of prostate cancer for men with and without a family history of the disease (13). Therefore, relative risk estimates derived from studies on younger men should not be multiplied with the lifetime risk in the population to achieve an estimate of the absolute lifetime risk.

Strengths of our study include the use of nationwide, population-based, high-quality register data with almost complete capture rates (10,11). The statistical precision of our calculations was therefore high. The narrow confidence intervals should not, however, be confused with high external validity. The incidences of any and high-risk prostate cancer vary geographically; the incidence of low-risk prostate cancer also changes over time because of varying diagnostic activity (PSA testing). The reported probabilities of any prostate cancer should be regarded as approximations of the probabilities for men only in populations with a high prostate cancer incidence and a high uptake of PSA testing, such as in North America, Australia, New Zealand, and north-western Europe. The incidence of high-risk prostate cancer is not much affected by PSA testing, so the reported probabilities of high-risk disease are applicable also for men in populations with a high incidence and a low uptake of PSA testing, such as in the Caribbean and in some parts of Africa. Moreover, despite the inclusion of more than 50000 men at risk in total, the number of men at risk before age 55 years was low in many of the subgroups. The confidence
Figure 5. Pictograms of the probabilities of no (white men), low-risk (light gray men), intermediate risk (dark gray men), and high-risk, including metastatic (black men), prostate cancer. A) Average population probabilities at age 65 years. B) Probabilities at age 65 years for men with a father and one brother with prostate cancer. C) Average population probabilities at age 75 years. D) Probabilities at age 75 years for men with a father and one brother with prostate cancer.
intervals of the probabilities shown in the figures for men younger than 55 years are therefore wider than the ones shown for men at age 65 years in Table 1.

Another limitation is that the sons of men registered in PCBaSe were too young to allow analysis of their cancer risk; only probabilities for the index men’s brothers were analyzed. The risk of prostate cancer for men whose father is the only affected family member is lower than the risk for men with an affected brother (3). A meta-analysis reported risk ratios of 2.4 for sons and of 3.1 for brothers of men with prostate cancer (3).

We had detailed, complete information on cancer characteristics at the time of diagnosis for the index cases’ brothers. No such detailed information was available to categorize the severity of the fathers’ cancers. The ad hoc nature of the criteria for these categories may have contributed to the lack of association between the fathers’ and their sons’ cancer risk categories. Moreover, the categorization of the brothers’ cancers was based on the diagnostic prostate biopsies only. As some men diagnosed with low-risk cancer have an undetected prostate cancer of higher grade, the tendency for aggressive prostate cancer to run in families may be stronger than suggested by our results.

To summarize, we used nationwide, population-based registers to calculate age-specific probabilities of any, non-low-risk, and high-risk prostate cancer for men with and without a known family history of prostate cancer. The probabilities of high-risk prostate cancer were substantially lower than of any prostate cancer. As the probability of any prostate cancer in populations with widespread PSA testing is inflated by clinically insignificant cancer, the probabilities of non-low- and high-risk prostate cancer are more appropriate for counseling men with a family history of prostate cancer. We suggest that age-specific probabilities of non-low- and high-risk cancer are incorporated in future clinical guidelines.

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References