Risk of prostate cancer in a population-based cohort of men with coeliac disease

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<td>Published Version</td>
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</table>
Risk of prostate cancer in a population-based cohort of men with coeliac disease

JF Ludvigsson*,1,2, K Fall3,4 and S Montgomery2,3,5

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BACKGROUND: Prostate cancer (PC) is a leading cause of fatal cancer in men in developed countries. Coeliac disease (CD) has previously been linked to a raised cancer risk, and changes in some exposures following a CD diagnosis might hypothetically raise PC risk.

METHODS: We identified 10,995 patients with CD who had undergone a small intestinal biopsy in 1969–2007. Statistics Sweden then identified 54,233 age-matched male reference individuals from the general population. PC data were obtained from the Swedish Cancer Register. Hazard ratios (HRs) for PC were estimated using Cox regression analysis.

RESULTS: During follow-up, 185 individuals with CD (expected n = 200) had an incident diagnosis of PC. This corresponds to a HR of 0.92 (0.79–1.08) (with 95% confidence interval) and an absolute risk reduction of 15/100,000 person-years among those with CD. An increased risk was not observed even when identification of PC began 5 years after biopsy.

CONCLUSION: Our conclusion is that a CD diagnosis does not represent an increased risk for PC.

Keywords: coeliac disease; cohort study; inflammation; prostate cancer

Prostate cancer (PC) is one of the leading causes of cancer mortality in men in industrialised countries (Ferlay et al., 2010). Established risk-factors for PC include increasing age, ethnic origin, and hereditary/familial factors. Although the great variability in incidence across different parts of the world can be attributed largely to differences in diagnostic intensity, the over 10-fold variation in mortality rates between low-risk countries in Asia and high-risk countries, such as Sweden (Ferlay et al., 2010), suggests that environmental factors, such as diet, may account for some of the observed variation (Shimizu et al., 1991; Hsing and Devesa, 2001).

Coeliac disease (CD) is an immune-mediated disease that occurs in 1% of the Western population (Dube et al., 2005). It is characterised by small intestinal inflammation and villous atrophy (VA) (Ludvigsson and Green, 2011). The only available treatment consists of a gluten-free diet where the individual avoids wheat, barley, and rye (Kupper, 2005), whereas consumption of oats is safe for patients with CD (Janatuinen et al., 1995).

Earlier research has shown a relative risk for PC in CD of 1.50 (95% CI: 0.98–2.30) (Askling et al., 2003; Card et al., 2004), but with no relative risks reported.

In this study, we tested the hypothesis that men with a diagnosis of CD have a higher risk of PC. This was tested using longitudinal Swedish register data for 10,995 men with CD and 54,233 age-matched men in the comparison cohort.

MATERIALS AND METHODS

We used national Swedish data from biopsy reports to identify patients with CD. These data were linked to the Swedish Cancer Register in order to examine the risk of PC.
Epidemiology

Before CD diagnosis (individuals with a diagnosis of PC before CD diagnosis (31 December 2007 (cancer data available until this date), were excluded). We also excluded controls that entered the study at this time. Finally, there was left one individual with CD whose matched index controls had a diagnosis of type 1 diabetes before the end of follow-up (n = 200), corresponding to a HR of 0.92 (95% CI = 0.79–1.08) (Table 2). The risk estimate did not change notably when we excluded individuals with a diagnosis of type 1 diabetes (0.93; 0.79–1.09). Nor did it change notably when we adjusted for country of birth (0.92; 0.78–1.07) or education (0.93; 0.78–1.12). When we excluded the first year of follow-up to minimise the risk of surveillance bias, the HR was little changed (0.89; 0.75–1.06). After 5 years of follow-up, giving sufficient time for an influence of the diet, the HR for PC in CD was 1.00 (Table 2).

The differences in PC risk by age at CD diagnosis were not statistically significant (P-value for interaction: 0.197) (Table 3). There were no notable differences in risk estimates for PC by calendar period (P-value for interaction: 0.926). When death due to PC, indicating more aggressive disease, was used as an alternative outcome (with 21 deaths among CD patients and an expected of 36), the HR for the association of CD with PC-related death remained below 1.00 (data not shown).

CD and subsequent PC

During follow-up, there were 185 diagnoses of PC (expected n = 200), corresponding to a HR of 0.92 (95% CI = 0.79–1.08) (Table 2). The risk estimate did not change notably when we excluded individuals with a diagnosis of type 1 diabetes (0.93; 0.79–1.09). Nor did it change notably when we adjusted for country of birth (0.92; 0.78–1.07) or education (0.93; 0.78–1.12). When we excluded the first year of follow-up to minimise the risk of surveillance bias, the HR was little changed (0.89; 0.75–1.06). After 5 years of follow-up, giving sufficient time for an influence of the diet, the HR for PC in CD was 1.00 (Table 2).

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**RESULTS**

**Background data**

The majority of the participants with CD had a biopsy from 1990 onwards and entered the study at this time, as did the matched comparison cohort. The median age at diagnosis of PC was 71 years in men with CD and 72 years in the comparison cohort. Other characteristics of the study participants are listed in Table 1. Some 3.8% of the individuals with CD but only 0.4% of the matched controls had a diagnosis of type 1 diabetes before the end of follow-up (P < 0.001, χ²-test).

**Statistics**

Cox regression was used to estimate relative risks. In our statistical model, we used internal stratification for age at the time of the first biopsy (and corresponding age in reference individuals), calendar period, and county. Our analysis therefore took into account the influence of age, calendar period, and county (similar to the effect of use of risk-sets in conditional logistic regression). Follow-up time started on the date of the first biopsy with VA and on the corresponding date in matched reference individuals. It ended with a diagnosis of PC, death, emigration, or on 31 December 2007, whichever came first. In reference individuals, follow-up could also end if the individual underwent a small intestinal biopsy. We used log-minus-log curves to test the proportional hazards assumption (Figure in Supplementary Appendix showing that this condition was fulfilled). We also evaluated the risk of PC stratified by follow-up time (<1 year, 1 to <5 years, and ≥5 years), sex, age at CD diagnosis (0–19, 20–39, 40–59, and ≥60 years at first biopsy), and calendar period of the first biopsy (1989, 1990–1999, and 2000 until present). Death due to PC (based on underlying cause of death according to death certificates) was used as an alternative outcome in a subanalysis in an attempt to identify a more aggressive PC phenotype. Incidence rates were calculated using the number of first PC events divided by the number of person-years at risk. The expected number of cases was derived from the observed number of cases divided by the hazard ratio (HR). In this way, the expected number of cases is based on the age and sex distribution of the CD cohort.

We identified individuals with type 1 diabetes using the Swedish Hospital Discharge Register (see Supplementary Appendix for ICD codes) (Ludvigsson et al. 2011). Type 1 diabetes is associated with CD (Bao et al., 1999; Smyth et al., 2008), but inversely associated with PC, so concomitant type 1 diabetes could therefore potentially hide a positive association between CD and PC. A subanalysis excluded all individuals with a diagnosis of type 1 diabetes, irrespective of when the diagnosis was made.

In another subanalysis, we adjusted for education using seven *a priori* educational categories determined by Statistics Sweden (<9 years, 9–10 years, ≤2 years of high school, ≥3 years of high school, <3 years of college/university, ≥3 years of college, and postgraduate studies). In a third subanalysis, we adjusted for country of birth (Nordic and non-Nordic countries).

Statistical significance defined as 95% CI for risk estimates not including 1.0. SPSS 18.0 software (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

**CD and subsequent PC**

During follow-up, there were 185 diagnoses of PC (expected n = 200), corresponding to a HR of 0.92 (95% CI = 0.79–1.08) (Table 2). The risk estimate did not change notably when we excluded individuals with a diagnosis of type 1 diabetes (0.93; 0.79–1.09). Nor did it change notably when we adjusted for country of birth (0.92; 0.78–1.07) or education (0.93; 0.78–1.12).

When we excluded the first year of follow-up to minimise the risk of surveillance bias, the HR was little changed (0.89; 0.75–1.06). After 5 years of follow-up, giving sufficient time for an influence of the diet, the HR for PC in CD was 1.00 (Table 2).

The differences in PC risk by age at CD diagnosis were not statistically significant (P-value for interaction: 0.197) (Table 3). There were no notable differences in risk estimates for PC by calendar period (P-value for interaction: 0.926).

When death due to PC, indicating more aggressive disease, was used as an alternative outcome (with 21 deaths among CD patients and an expected of 36), the HR for the association of CD with PC-related death remained below 1.00 (data not shown).

**DISCUSSION**

This study found no association between CD and PC using longitudinal data. It is one of the first large-scale studies of this subject and it used histology from intestinal biopsies to identify CD reliably. Our findings are consistent with the two general population-based studies from England (Goldacre et al., 2008) and
Sweden (Askling et al, 2002), although this study had substantially more statistical power to detect an association.

Although earlier studies on CD and PC have been based on as few as 2–14 positive events (Askling et al, 2002; Anderson et al, 2007; Goldacre et al, 2008), we observed 185 PC diagnoses in our study, allowing for stratification and greater precision.

CD patients in our cohort were ascertained through biopsy reports, so they are more likely to have typical CD characteristics than those identified through inpatient registers as this may signal comorbidity (Askling et al, 2002; Goldacre et al, 2008), because CD investigation does not require hospital care. Most adult gastroenterologists (96%) and all paediatricians obtain biopsies from the majority of patients with suspected CD (over 90%) to make the diagnosis. Therefore, diagnosis of CD among our study population is highly reliable. Small intestinal biopsies with VA have high specificity for CD. When two independent researchers examined more than 1500 biopsy reports with VA or inflammation, <0.3% of patients suffered from inflammatory bowel disease, which was the most common comorbidity (other than CD) (Ludvigsson et al, 2009a). Patients with CD are at increased risk of comorbid type 1 diabetes. We performed an analysis where all the individuals with a diagnosis of type 1 diabetes before the end of follow-up were excluded. This exclusion did not affect the risk estimates for PC.

### Table 1 Characteristics of the study participants

<table>
<thead>
<tr>
<th>Age and follow-up</th>
<th>Matched controls</th>
<th>Patients with CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>54,233</td>
<td>10,995</td>
</tr>
<tr>
<td>Age at study entry, years (median, range)</td>
<td>34; 0–95</td>
<td>35; 0–95</td>
</tr>
<tr>
<td>Age 0–19 (%)</td>
<td>21,734 (40.1)</td>
<td>4356 (39.6)</td>
</tr>
<tr>
<td>Age 20–39 (%)</td>
<td>8216 (15.1)</td>
<td>1659 (15.1)</td>
</tr>
<tr>
<td>Age 40–59 (%)</td>
<td>12,946 (23.9)</td>
<td>2605 (23.7)</td>
</tr>
<tr>
<td>Age ≥60 (%)</td>
<td>11,337 (20.9)</td>
<td>2375 (21.6)</td>
</tr>
<tr>
<td>Follow-up, years (median, range)</td>
<td>8; 0–39</td>
<td>8; 0–37</td>
</tr>
<tr>
<td>Follow-up, years (mean ± SD)</td>
<td>9.5 ± 6.4</td>
<td>9.3 ± 6.4</td>
</tr>
<tr>
<td>Calendar year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1988 (%)</td>
<td>8101 (14.9)</td>
<td>1643 (14.9)</td>
</tr>
<tr>
<td>1990–1999 (%)</td>
<td>22,824 (42.1)</td>
<td>4627 (42.1)</td>
</tr>
<tr>
<td>2000– (%)</td>
<td>23,308 (43.0)</td>
<td>4725 (43.0)</td>
</tr>
<tr>
<td>Covariates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic country of birth (%)</td>
<td>51,241 (94.5)</td>
<td>10,662 (97.0)</td>
</tr>
<tr>
<td>Type 1 diabetes (%)</td>
<td>208 (0.4)</td>
<td>418 (3.8)</td>
</tr>
</tbody>
</table>

Abbreviation: CD = coeliac disease. *Follow-up time until diagnosis of prostate, death from other cause, emigration, or 31 December 2007. In reference individuals, follow-up could end if the patients underwent a small intestinal biopsy. 1Sweden, Denmark, Finland, Norway, and Iceland.

### Table 2 Risk of prostate cancer by follow-up time

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Absolute risk/100,000 PYAR</th>
<th>Excess risk/100,000 PYAR</th>
<th>Attributable percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>185</td>
<td>200</td>
<td>0.92</td>
<td>0.79–1.08</td>
<td>0.336</td>
<td>182</td>
<td>–15</td>
<td>–8</td>
</tr>
<tr>
<td>Year &lt; 1</td>
<td>22</td>
<td>18</td>
<td>1.23</td>
<td>0.78–1.96</td>
<td>0.374</td>
<td>204</td>
<td>39</td>
<td>19</td>
</tr>
<tr>
<td>1–4.99</td>
<td>48</td>
<td>67</td>
<td>0.71</td>
<td>0.53–0.97</td>
<td>0.030</td>
<td>133</td>
<td>–54</td>
<td>–40</td>
</tr>
<tr>
<td>5+</td>
<td>115</td>
<td>115</td>
<td>1.00</td>
<td>0.82–1.23</td>
<td>0.085</td>
<td>209</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio; PYAR = person-years at risk. Reference is general population comparator cohort. The attributable percentage was calculated as (1 – 1/HR).

One weakness of this study is the lack of individual data on dietary components or compliance to a gluten-free diet. Some aspects of dietary compliance could theoretically raise the risk of PC, although mucosal healing and less chronic inflammation might reduce the risk. In a validation study of 121 randomly selected individuals with VA, there were indications of low dietary compliance in 15/86 individuals (17, 95% CI 9–25%), thus with dietary compliance in 83% (Ludvigsson et al, 2009a). This study found no association between CD and PC (HR = 0.92).

As PC may have a prolonged natural history (Schmid et al, 1993), we also examined risk of PC according to time since diagnosis of CD. Although there was no association between CD and PC in the first year beyond biopsy, or more than 5 years after biopsy, there was a statistically significant reduced risk of PC 1–5 years after CD diagnosis. We cannot rule out that there is a true decreased risk of PC in CD due to factors, such as lower body mass index (BMI) in patients with CD (Discacciati et al, 2011). In the first year after diagnosis, this may be masked by an increased ascertainment rate of PC as comorbid conditions are more likely to be detected during diagnosis or treatment. With time, the lower PC risk may not persist as mucosal healing results in increased BMI. It should be noted that the apparent reduced risk 1–5 years after CD diagnosis could represent a chance finding.

Although the total follow-up time for patients with CD in this study was 101,000 person-years, we did not have enough follow-up to estimate the risk of PC in CD diagnosed in childhood. It has been suggested that an early diagnosis of CD in childhood may protect against certain cancers (Elfstrom et al, 2011), but as participants in this study tended to receive a later diagnosis, this putative protection against cancer could not have a positive association. Other immune-mediated diseases, such as type 1 diabetes (Kasper et al, 2009; Shu et al, 2010), ulcerative colitis (Goldacre et al, 2008), Crohn’s disease (Goldacre et al, 2008), and Wegener’s granulomatosis have been inversely associated with PC (Knight et al, 2002). This study found no association between CD and PC.

Also, adolescence represents a critical window of prostate development, where diet (Andersson et al, 1995) and hormonal exposure (Barba et al, 2008) could be important. Although we could investigate participants with a CD diagnosis in childhood, it is important to emphasise that there was no evidence of increased PC risk among men diagnosed with CD from age 40 years: this study would have been able to detect such a risk. This indicates that middle-aged men who receive a diagnosis of CD need not be concerned that the diagnosis, or dietary changes typically associated with it, could increase their risk of PC.

Another potential weakness is our lack of data on BMI. High BMI has been inversely associated with CD (Olen et al, 2009), but positively associated with PC (Moller et al, 1994), although most prospective studies do not support this association (Rodriquez et al, 2007; Wright et al, 2007). Neither did we have any data on smoking. Smoking may increase the risk of PC (Plaskon et al, 2007). Although several studies have indicated an inverse relationship between smoking and CD (Vazquez et al, 2001; Austin et al, 2002),
a recent study by our group found a nonsignificantly increased risk for later CD in smokers (adjusted Odds ratio = 1.25; 95% CI = 0.94 – 1.67) (Ludvigsson et al., 2005). Although unlikely, we cannot rule out the possibility that lower BMI and a lack of smoking among individuals with CD may have hidden a modest association between CD and PC.

PSA-testing has, since it was introduced during the 90s, resulted in a rising overdiagnosis of PC (i.e., detection of nonlethal pseudotumours) and it is becoming increasingly important to separate clinically significant PC from indolent disease in aetiological studies. The Swedish Cancer Registry covers essentially all incident PCs, but lacks information on tumour stage and Gleason grade. Although PSA-screening is less common in Sweden than in the United States and many other Western countries, around 40% of the cases were diagnosed with screening-detected PC in Sweden during the latter part of the study period (National Prostate Cancer Register, http://www.roc.se/prostata.asp). We tackled this through a subanalysis that used death due to PC as the outcome to identify cases were diagnosed with screening-detected PC in Sweden.

In conclusion, patients with CD seem to be at no increased risk of PC.

Ethical approval

This project (2006/633–31/4) was approved by the Research Ethics Committee of the Karolinska Institute, Sweden on 14 June 2006.

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Disclaimer

Independence (role of the sponsors): None of the funders had any role in the design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)

Table 3 Risk of prostate cancer (subgroup analyses)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Observed events</th>
<th>Expected events</th>
<th>HR</th>
<th>95% CI</th>
<th>P-value</th>
<th>Absolute risk/100 000 PYAR</th>
<th>Excess risk/100 000 PYAR</th>
<th>Attributable percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–19</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>—</td>
<td>1.00</td>
<td>0.69 – 1.33</td>
<td>0.841</td>
<td>10</td>
</tr>
<tr>
<td>20–39</td>
<td>3</td>
<td>1</td>
<td>3.05</td>
<td>0.74 – 12.56</td>
<td>0.123</td>
<td>18</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>40–59</td>
<td>71</td>
<td>69</td>
<td>1.03</td>
<td>0.79 – 1.33</td>
<td>0.841</td>
<td>285</td>
<td>7</td>
<td>3</td>
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<tr>
<td>60+</td>
<td>111</td>
<td>131</td>
<td>0.85</td>
<td>0.69 – 1.04</td>
<td>0.118</td>
<td>744</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Calendar period</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1989</td>
<td>49</td>
<td>50</td>
<td>0.97</td>
<td>0.71 – 1.34</td>
<td>0.873</td>
<td>164</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1990–1999</td>
<td>95</td>
<td>103</td>
<td>0.92</td>
<td>0.74 – 1.15</td>
<td>0.464</td>
<td>181</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2000–</td>
<td>41</td>
<td>46</td>
<td>0.89</td>
<td>0.64 – 1.24</td>
<td>0.504</td>
<td>211</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Abbreviations: CI = confidence interval; HR = hazard ratio; PYAR = person-years at risk. Reference is general population comparator cohort. The attributable percentage was calculated as (1 – 1/HR).

REFERENCES


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