Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial

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BACKGROUND: The Prostate Cancer Prevention Trial has shown a protective effect of finasteride on prostate cancer in low-risk men. It is uncertain whether similar results can be expected when finasteride is used to treat benign prostatic hyperplasia.

METHODS: We performed an observational cohort study within the Finnish Prostate Cancer Screening Trial. Using a comprehensive prescription database on medication reimbursements during 1995–2004 of men using finasteride or alpha-blockers for benign prostatic hyperplasia, we evaluated prostate cancer incidence among 23 320 men screened during 1996–2004.

RESULTS: Compared to medication non-users, overall prostate cancer incidence was not significantly affected in finasteride users (hazard ratio 0.87; 95% CI 0.63–1.19). Incidence of Gleason 2–6 tumours, however, was decreased among finasteride users (HR 0.59; 95% CI 0.38–0.91), whereas incidence of Gleason 7–10 tumours was unchanged (HR 1.33; 95% CI 0.77–2.30). The protective effect concerned mainly screen-detected tumours. Overall prostate cancer risk was not significantly reduced among alpha-blocker users relative to non-users, but decreased incidence of high-grade tumours was observed (0.55; 95% CI 0.31–0.96).

CONCLUSIONS: The detection of low-grade, early-stage tumours is decreased among men who use finasteride for symptomatic BPH. The protective effect of finasteride can also be expected in men with benign prostatic hyperplasia.

British Journal of Cancer (2009) 101, 843–848. doi:10.1038/sj.bjc.6605188 www.bjcancer.com

Published online 4 August 2009
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Keywords: alpha-blockers; benign prostatic hyperplasia; finasteride; epidemiology; prostatic neoplasms; screening

Finasteride, a 5α-reductase enzyme-inhibitor that inhibits conversion of testosterone into active androgen metabolite dihydrotestosterone, thereby lowering prostate volume and serum prostate-specific antigen (PSA) level (Marberger, 2006), is used for treatment of benign prostatic hyperplasia (BPH) and male pattern baldness. The Prostate Cancer Prevention Trial (PCPT) has reported a 25% decrease in prostate cancer incidence in men receiving finasteride compared with placebo (Thompson et al, 2003). The trial participants had baseline PSA 3.0 ng ml−1 or less and low symptom score of lower urinary tract symptoms (LUTS). The restrictive inclusion criteria limit the generalisability of the findings. It is not known whether the results are applicable to men using finasteride for symptomatic BPH.

α1-Adrenoceptor antagonists (alpha-blockers) are used in the medical management of symptoms of benign prostatic hyperplasia. Alpha-blockers lower smooth muscle tension in the prostate and urinary tract, thereby improving urinary flow and decreasing LUTS (Ishizuka et al, 2002). Some experimental studies have reported increased prostate cancer cell apoptosis after treatment with quinazoline-derived alpha-blockers, terazosin and doxazosin (Kyriakou and Benning, 2006; Benning and Kyriakou, 2002).

One cohort study has reported a decreased incidence among alpha-blocker users (Harris et al, 2007).

We evaluated the effect of finasteride and alpha-blocker usage on prostate cancer incidence in a cohort of men participating in the screening arm of the Finnish Prostate Cancer Screening Trial during 1996–2004.

MATERIALS AND METHODS

The Finnish Prostate Cancer Screening Trial is a part of the European Randomized Study of Prostate Cancer Screening. The trial assesses whether screening can reduce prostate cancer mortality (Määttänen et al, 1999) The ethical committees of each participating hospital approved the study protocol. In 1996–1999, all men aged 55–67 years and residing in the metropolitan areas of Helsinki and Tampere (80 484 men) were identified from the population register of Finland and randomly assigned into either the screening arm (32 000 men) or the control arm (48 484 men) of the trial. The detailed protocol has been described previously (Määttänen et al, 1999). For exclusion of prevalent prostate cancer cases at randomisation, the cohort was linked to the comprehensive Finnish Cancer Registry (Teppo et al, 1994).

Men in the screening arm were recruited with mailed invitations to undergo a PSA screening test at 4-year intervals. After a written informed consent, a blood sample was drawn. All participants also filled in a questionnaire on prostate cancer family history and
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British Journal of Cancer (2009) 101(5), 843 – 848

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amount (daily doses) and duration (in years) of medication use were analysed as time-dependent covariates. In analyses stratified by cumulative amount/duration of medication use, the users contributed person time in lower stratum until reaching the cut-point for upper stratum.

Trends in incidence by amount or duration of medication use were tested by adding these indicators into Cox regression model as continuous covariates.

The proportional hazards assumption was tested by adding the interaction term for finasteride or alpha-blocker use and person time to the model. The term was not statistically significant by the likelihood ratio test, confirming the assumption. All analyses were performed using SPSS 15.0 statistical software.

RESULTS

Of the 23 320 men in the cohort, 1754 (7.5%) had used finasteride and 3848 (16.5%) had used either tamsulosin or alfuzosin. Prevalence of medication use increased with age at start of follow-up. Family history was comparable in the two groups (Table 1). The age-standardised median PSA was higher among BPH medication users compared with non-users (Table 1). Both finasteride and alpha-blocker use was associated with a decreased proportion of free PSA, the effect again being stronger in finasteride users. Among the men attending the third screening round, average prostate volumes and the median BMI were higher among medication users than non-users (Table 1).

Overall, finasteride use was not significantly associated with risk (HR 0.87, 95% CI 0.63–1.19; Table 2). However, the risk of low-grade (Gleason 2–6) tumours was decreased among finasteride users (HR 0.59; 95% CI 0.38–0.91) and further diminished in risk in relation to the cumulative amount and duration of medication usage (P for trend = 0.004 and 0.019, respectively; Table 2). Generally, incidence of high-grade, organ-confined or advanced stage tumours was not affected by finasteride usage (Table 2). However, among long-term finasteride users, increased incidence of high-grade tumours was observed (HR 2.49; 95% CI 1.27–4.89 for men who had used at least 1087 doses of finasteride). Overall risk did not differ between alpha-blocker users and non-users. However, lowered incidence of high-grade tumours was observed (HR 0.55; 95% CI 0.31–0.96), with a decreasing trend in risk with cumulative duration of alpha-blocker use (Table 3).

In an analysis stratified by serum PSA concentration, prostate cancer risk was decreased in finasteride and alpha-blocker users with PSA ≥ 4 ng mL⁻¹ (the cut-off value for screen-positive test, i.e., indication for prostate biopsy; Table 4). The point estimate was lower among finasteride users, but the confidence intervals overlap. The decreased risk was driven by the lower incidence of screen-detected tumours among these men. Risk of interval cancers, that is, tumours diagnosed between the screening rounds, was not significantly affected in finasteride users. However, among alpha-blocker users with PSA below 4 ng mL⁻¹, the risk of interval cancer was increased (HR 2.46; 95% CI 1.21–5.00).

DISCUSSION

In our cohort study within the screening arm of the Finnish Prostate Cancer Screening Trial we found a reduced risk of low-grade prostate cancer among finasteride users, among whom an increased risk of high-grade cancers was seen among long-term users. These findings confirm previous findings on this topic, but provide wider generalisability than the Prostate Cancer Prevention Trial, and improved internal validity compared with non-randomised studies due to comprehensive and systematic case ascertainment. Alpha-blocker usage generally did not affect incidence, but some evidence for a decreased risk of high-grade tumours was observed.
Table 1  Characteristics of users and non-users of finasteride and alpha-blockers in the Finnish Prostate Cancer Screening Trial

| Characteristics: | Finasteride usage | Alpha-blocker usage* |
|------------------|-------------------|----------------------|
|                  | Yes | No | Yes | No |
| Participants (n) | 1754 | 21 566 | 3848 | 19 472 |
| Age at randomisation (years) | 63 | 476 (9.2) | 4674 (90.8) | 1025 (19.9) | 4125 (80.1) |
| Prevalence of family history of prostate cancer (%)b | 0.3 | 0.3 | 0.4 | 0.3 |
| Mean no. of screening rounds attended | 2.0 | 1.9 | 2.0 | 1.9 |
| Geometric mean of PSA (95% CI)c | 1.58 (0.24 – 11.05) | 1.22 (0.27 – 7.72) | 1.60 (0.28 – 9.46) | 1.22 (0.26 – 7.67) |
| Cumulative amount of medication usea | 1.19 (0.27 – 6.42) | 1.49 (0.23 – 8.94) | 1.60 (0.28 – 9.46) | 1.49 (0.23 – 8.94) |
| 1st quartile | 1.95 (0.31 – 12.94) | — | 1.54 (0.26 – 8.64) | — |
| 2nd quartile | 1.72 (0.19 – 9.56) | — | 1.66 (0.19 – 9.07) | — |
| 3rd quartile | 1.49 (0.23 – 8.94) | — | 1.58 (0.29 – 9.58) | — |
| 4th quartile | 1.31 (0.17 – 1.25) | — | 1.80 (0.36 – 11.65) | — |
| Geometric mean of % free PSA (95% CI)e | 22.37 (9.49 – 48.36) | 26.48 (10.40 – 52.80) | 25.26 (10.56 – 50.96) | 26.43 (10.30 – 52.80) |
| Cumulative amount of medication usea | 26.2 | 26.4 | 26.2 | 26.2 |
| 1st quartile | 22.87 (10.96 – 45.40) | — | 25.26 (10.50 – 50.99) | — |
| 2nd quartile | 22.67 (9.13 – 47.26) | — | 24.66 (9.90 – 47.47) | — |
| 3rd quartile | 21.22 (9.35 – 48.59) | — | 25.36 (10.85 – 54.85) | — |
| 4th quartile | 21.12 (7.75 – 43.57) | — | 25.76 (10.76 – 52.53) | — |
| Median body mass index | 26.7 | 26.2 | 26.6 | 26.2 |
| Median prostate volume (ml)f | 49 | 36 | 42 | 36 |

*Includes users of tamsulosin and alfuzosin. bFather, brother or son diagnosed with prostate cancer prior to initiation of the Finnish Prostate Cancer Screening Trial. cAge-standardised values. dAs measured by a urologist on a transrectal ultrasound examination. eNon-users 1.22 (0.27–7.72) Non-users 1.22 (0.26–7.67) fAs measured by a urologist on a transrectal ultrasound examination.

Availability of comprehensive and detailed information on medication purchases from the SII prescription database allowed us to evaluate BPH medication usage accurately and in an unbiased fashion. Finasteride, tamsulosin and alfuzosin were available in Finland only through the physician’s prescription during the study period, so their purchase is comprehensively documented by the prescription database.

Our finding of a decreased risk of low-grade tumours among finasteride users is similar with the results from the Prostate Cancer Prevention Trial (Thompson et al., 2003). However, a major limitation of our study in comparison to PCPT is that this is a non-experimental study without any intervention related to BPH care, a conclusion supported by a previous case–control study (Irani et al., 2002). Unlike PCPT, we did not observe a significant decrease in overall risk among finasteride users, although the relative risk reduction in our study (22%) was close to that reported in the PCPT (25%). However, among the biopsied (screen-positive) men, the overall risk decrease was also significant in our study. It should be noted that the average duration and cumulative amount of finasteride usage was lower in our study than in the PCPT.

In this study, finasteride users had symptomatic BPH, and confounding by indication could affect the results, if BPH affects the risk of prostate cancer or additional testing in the clinical setting would affect prostate cancer detection. In this case, a positive association between BPH and prostate cancer and further PSA tests would be expected to increase detection. In our study, the contrary was observed, so BPH as indication for finasteride usage cannot account for our findings. Unlike the PCPT trial (Thompson et al., 2003), we did not observe overall risk increase for high-grade prostate tumours among finasteride users. However, the risk was increased among long-term users, although no dose dependence between cumulative dose or duration of finasteride use and risk of high-grade cancer was observed. Later analyses of the PCPT results...
have shown that the observed higher proportion of high-grade cancers in finasteride-treated men is due to detection bias caused by decreased prostate volume, increased sensitivity of PSA to detect prostate cancer and altered tumour grading in finasteride users (Thompson et al., 2006; Lucia et al., 2007; Pinsky et al., 2008).

This effect could also have caused the slightly increased incidence of high-grade tumours in our study.

Use of alpha-blockers tamsulosin and alfuzosin had no effect on overall risk, but there was some indication of a reduced risk of high-grade tumours. Previously, quinazoline-derived alpha-

Table 2  Hazard ratio for prostate cancer by amount and duration of use of finasteride and by prostate cancer stage and grade, Finnish Prostate Cancer Screening Trial

| Quantity/duration of medication use | Overall | Gleason ≤ 6 | Gleason 7 – 10 | Organ-confined tumours a | Advanced tumours b |
|------------------------------------|---------|-------------|---------------|-------------------------|------------------|
| **Finasteride**                    |         |             |               |                         |                  |
| Non-users                          | 1507    | Reference   | 1139          | Reference               | 338              | Reference       |
| All users                          | 87      | 0.87 (0.63 – 1.19) | 55           | 0.59 (0.38 – 0.91)     | 26               | 1.33 (0.77 – 2.30) |
| **Cumulative quantity of finasteride use (daily doses) c** | | | | | |
| 28 – 180                           | 34      | 1.34 (0.74 – 2.42) | 24           | 0.80 (0.33 – 1.92)     | 6                | 1.17 (0.29 – 4.74) |
| 181 – 398                          | 21      | 0.91 (0.50 – 1.65) | 14           | 0.76 (0.36 – 1.60)     | 5                | 0.79 (0.20 – 3.20) |
| 399 – 1086                         | 17      | 0.57 (0.27 – 1.19) | 13           | 0.64 (0.29 – 1.43)     | 4                | 0.37 (0.05 – 2.68) |
| > 1087                             | 15      | 0.82 (0.47 – 1.46) | 4            | 0.28 (0.09 – 0.87)     | 11               | 2.49 (1.27 – 4.89) |
| **P** trend                         | 0.204   |             | 0.009         |                         | 0.114            |                  |
| **Years of finasteride use d**     |         |             |               |                         |                  |                  |
| 1                                  | 41      | 0.89 (0.5 – 1.48) | 30           | 0.62 (0.31 – 1.24)     | 7                | 0.57 (0.14 – 2.32) |
| 2                                  | 19      | 0.96 (0.50 – 1.85) | 13           | 0.84 (0.38 – 1.88)     | 5                | 1.02 (0.25 – 4.13) |
| 3 – 4                              | 11      | 0.72 (0.39 – 1.35) | 7            | 0.48 (0.20 – 1.16)     | 4                | 1.60 (0.66 – 3.91) |
| > 4                                | 16      | 1.00 (0.47 – 2.11) | 5            | 0.40 (0.10 – 1.61)     | 10               | 2.61 (1.06 – 6.45) |
| **P** trend                         | 0.411   |             | 0.019         |                         | 0.057            | 0.524            |

aMen with T1N0M0 and T2N0M0 tumours combined. bMen with stage T3N0M0, T3N1M0, T4N0M0 or T1–4,N1M1 tumours combined. cFrom Cox proportional hazard regression adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000). dStratification in quartiles of cumulative quantity/duration of finasteride use. eEstimated by including cumulative dose (DDDs) or duration (years) of medication use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amount of medication use.

Table 3  Hazard ratio for prostate cancer by amount and duration of use of alpha-blockers and by prostate cancer stage and grade, Finnish Prostate Cancer Screening Trial

| Quantity/duration of medication use | Overall | Gleason ≤ 6 | Gleason 7 – 10 | Organ-confined tumours a | Advanced tumours b |
|------------------------------------|---------|-------------|---------------|-------------------------|------------------|
| **Alpha-blockers**                 |         |             |               |                         |                  |
| Non-users                          | 1399    | Reference   | 1041          | Reference               | 330              | Reference       |
| All users                          | 195     | 1.05 (0.85 – 1.31) | 153           | 1.20 (0.94 – 1.52)     | 34               | 0.55 (0.31 – 0.96) |
| **Cumulative quantity of alpha-blockers use (daily doses) e** | | | | | |
| 10 – 60                            | 77      | 1.25 (0.83 – 1.87) | 62           | 1.65 (1.09 – 2.49)     | 12               | 0.21 (0.03 – 1.52) |
| 61 – 180                           | 46      | 1.00 (0.64 – 1.56) | 35           | 0.84 (0.46 – 1.49)     | 8                | 0.95 (0.39 – 2.30) |
| 181 – 629                          | 39      | 1.11 (0.75 – 1.64) | 30           | 1.21 (0.77 – 1.88)     | 8                | 0.64 (0.24 – 1.72) |
| > 630                              | 33      | 0.89 (0.59 – 1.36) | 26           | 1.12 (0.72 – 1.75)     | 6                | 0.40 (0.13 – 1.25) |
| **P** trend                         | 0.975   |             | 0.345         |                         | 0.053            | 0.700           |
| **Years of alpha-blockers use d**  |         |             |               |                         |                  |                  |
| 1                                  | 111     | 1.00 (0.73 – 1.38) | 86           | 1.08 (0.75 – 1.55)     | 19               | 0.60 (0.27 – 1.35) |
| 2                                  | 43      | 1.46 (1.00 – 2.15) | 36           | 1.67 (1.09 – 2.56)     | 5                | 0.60 (0.19 – 1.89) |
| 3 – 4                              | 23      | 0.87 (0.55 – 1.37) | 15           | 1.04 (0.63 – 1.70)     | 8                | 0.48 (0.15 – 1.52) |
| > 4                                | 18      | 0.88 (0.42 – 1.86) | 16           | 1.15 (0.51 – 2.60)     | 2                | 0.38 (0.05 – 2.73) |
| **P** trend                         | 0.858   |             | 0.186         |                         | 0.044            | 0.580           |

aMen with T1N0M0 and T3N0M0, T4N0M0 tumours combined. bMen with stage T3N1M1, T4N0M0 or T1–4,N1M1 tumours combined. cFrom Cox proportional hazard regression adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000). dStratification in quartiles of cumulative quantity/duration of alpha-blocker use. eEstimated by including cumulative dose (DDDs) or duration (years) of medication use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amount of medication use.
blocks, terazosin and doxazosin, have been reported to inhibit prostate cancer cell growth and reduce incidence (Kyprianou and Benning, 2000; Benning and Kyprianou, 2002; Harris et al., 2007). Our results suggest that tamsulosin and alfuzosin could have similar effects but this aspect needs further research.

PCPT reported decreased serum PSA concentrations in finasteride users as compared with non-users (Etizioni et al., 2005). In our study, instead, serum PSA was increased in both finasteride and alpha-blocker users. Odds of having serum PSA exceeding the prostate biopsy cut-point (4 ng ml\(^{-1}\)) was not decreased, but conversely increased in finasteride users (OR 2.37; 95% CI 2.13–2.64). This is due to the fact that in our study these medications were used for BPH treatment and men using them are not comparable with non-users. Therefore, these differences reflect the effect of BPH, and not medications. However, the PSA concentration tended to decrease with increasing cumulative amount of finasteride use, although the geometric mean PSA remained above non-users even among men in the highest quartile of finasteride use (1087 doses or more), though the confidence intervals were wide (Table 1). A similar association was observed with increasing duration of finasteride use (results not shown). For alpha-blockers, the geometric mean PSA was constantly higher among users than non-users with no decrease by duration or amount of use. The decrease in the proportion of free PSA was more pronounced in finasteride users and increased in relation with amount and duration of medication use, probably reflecting its effect on proportion of free PSA in long-term use, as such relation was not observed in alpha-blocker users.

Both finasteride and alpha-blocker use was associated with a decreased risk of screen-detected tumours among screen-positive men. As the risk decrease was observed among users of both drug groups, it may be due to the underlying disease, BPH. PSA elevation in men with LUTS (medication users) is often caused by prostate enlargement, whereas in men with no such symptoms (medication non-users) PSA increase is more commonly caused by a prostate cancer. Alpha-blocker users, whose PSA was below 4 ng ml\(^{-1}\), were at increased risk between the screening rounds. The finding is consistent with our results from the previous case–control study (Murtola et al., 2007) and may reflect a similar mechanism. The Finnish guideline for clinical management of BPH recommends using alpha-blockers if a man has significant LUTS but no prostate enlargement (Finnish Medical Society Duodecim). Symptoms lead to clinical examinations and thus possibly to diagnosis despite the negative screening test. Additionally, men with significant LUTS may undergo transurethral resection of the prostate, in which incidental prostate cancer is a common finding (Merrill and Wiggins, 2002). This would lead to a bias of greater cancer detection in alpha-blocker users but not in finasteride users, as finasteride reduces the need for surgical management of BPH (Roehrborn et al., 2004).

We were able to control the confounding caused by age and familial predisposition (Crawford, 2003) in the analysis. Confounding by ethnicity (Crawford, 2003) is likely minimal due to the homogeneity of the Finnish population with over 98 percent of the population being of Finnish ancestry (Statistics Finland). Additionally, we had information on prostate volume and BMI for a proportion of our study population. Adjustment for these variables did not materially affect the results.

Our study has some limitations. The number of stage T1c, stage T2a lymph node-positive or metastatic tumours was small in our study population of screened men, limiting our inference concerning the risk of advanced cancer. Similarly, we could not analyse mortality among finasteride users due to the small number of deaths.

We did not have information on less established prostate cancer risk factors such as dietary patterns or nutrient intake (such as selenium or vitamin E). Medication users may be more health conscious than non-users, and follow a healthier diet, which could have reduced the incidence in medication users.

Some exposure misclassification was likely caused by the fact that the cohort follow-up started in 1996 at the earliest, though finasteride was licensed in Finland in 1992. Additionally, SI does not reimburse finasteride prescribed for treatment of androgenic alopecia, and thus we did not have information on finasteride use for this indication. Therefore, some of the finasteride users likely have longer history of use than appeared in our study, a bias that may have weakened the observed association with prostate cancer risk.

The decreased risk among finasteride users in a cohort of men participating in the Finnish Prostate Cancer Screening Trial suggest that finasteride has a clinically significant preventive effect against low-grade tumours also when used for treatment of symptomatic benign prostatic hyperplasia. Future research should aim to evaluate whether finasteride can reduce mortality.

### ACKNOWLEDGEMENTS

This study was supported by grants from Academy of Finland (205 862); Sigrid Juselius Foundation; the Finnish Cancer Society; Pirkanmaa Regional Fund of the Finnish Cultural Foundation; Medical Research Fund of Tampere University Hospital; the Finnish Cancer Organisations. The work of TJ Murtola has also been supported by Competitive Research Funding of Central Finland Central Hospital District, The Finnish Medical Society Duodecim and non-restricted grants from Astellas, Pfizer, Coloplast, research foundation of Orion Pharma and Abbott Pharma. We thank Dr Roger Rittmaster for his helpful comments during preparation of this article.
