Effects of dutasteride on prostate cancer incidence: A systematic review and meta-analysis

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ABSTRACT

5-Alpha-reductase inhibitors (5-ARIs) are used in the treatment of benign prostate hypertrophy (BPH). 5-ARIs, such as finasteride and dutasteride, suppress the biosynthesis of dihydrotestosterone (DHT), a precursor of androgen, which is closely related to the incidence of prostate cancer (PCa). A previous meta-analysis demonstrated a relationship between finasteride use and the incidence of PCA. However, there have been no meta-analyses on the relationship between PCa and dutasteride alone. This meta-analysis was performed to examine the prevalence of PCa in adult males taking dutasteride. We searched PubMed for reports regarding PCa risk and dutasteride use. The study was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses. The analytic hierarchy process (AHP) method was used to weight the studies. Odds ratios (ORs), 95% confidence intervals (CIs), and P-values were calculated using fixed- and random-effects models. A total of eight articles were included in the meta-analysis. The overall OR for both the fixed- and random-effects models was 0.669 and the 95% CI for the random-effects model (0.526–0.851; P = 0.006) was wider than that for the fixed effects model (0.548–0.817; P < 0.001). This study confirmed that the incidence of PCa was significantly reduced by taking dutasteride.

INTRODUCTION

5-Alpha-reductase inhibitors (5-ARIs), such as finasteride and dutasteride, are used to treat benign prostate hypertrophy (BPH) (Burnett and Wein, 2006; Liang et al., 2012). These drugs prevent the conversion of testosterone to dihydrotestosterone (DHT) and are known to be closely related to the incidence of prostate cancer (PCa) (Wurzel et al., 2007). Previous studies showed that a reduction in the level of DHT, the androgen precursor, decreased the risk of PCa (Roehrborn et al., 2002; Ross et al., 2012). On the other hand, the US Food and Drug Administration (FDA) does not recommend 5-ARIs as a treatment for PCa because of their potential to increase the incidence and recurrence rates of PCa, and PCa-related mortality (Azoulay et al., 2015; USFDA, 2020).

However, some randomized clinical trials reported that 5-ARI drugs reduced PCa risk (Roehrborn et al., 2011; Rompay et al., 2019). A previous meta-analysis demonstrated a link between finasteride
This study was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses (Moher et al., 2009). We performed a literature search using PubMed. The search terms for dutasteride were “dutasteride” and “dutasteride capsules.” The search terms for PCa were “prostate cancer,” “PCa,” “prostate carcinoma,” and “prostate malignancy.” All types of articles were searched for, and the reference sections of relevant systemic reviews were searched manually.

**Selection criteria**

Papers providing data about the relationship between dutasteride and PCa were included if they had sufficient data, such as the number of patients in the intervention and control groups, and the numbers of cases and non-cases, to calculate the odds ratio (OR) or relative risk (RR).

**Exclusion criteria**

Studies were excluded if they were related to PCa recurrence rather than incidence; included patients with current or previous PCa, or were duplicate publications.

**Statistical analysis**

MATERIALS AND METHODS

**Literature search**

The image contains a PRISMA flow diagram illustrating the process of identifying, screening, and selecting studies for the meta-analysis. The diagram shows the following steps:

1. **Identification**
   - Potentially relevant records identified through PubMed (N=351)

2. **Screening**
   - Records after duplicates removed (N=346)
   - Excluded (N=309):
     - No dichotomous data
   - Systemic review reference (N=3)

3. **Eligibility**
   - Records identified through literature search (N=37)
   - Excluded (N=29):
     - No association Dutasteride (10)
     - No association PCa incidence (4)
     - Out of subject (9)
     - Recruits are already PCa patients (3)
     - Associated with recurrence (1)
     - No data (1)
     - Duplicate (1)

4. **Included**
   - Studies included in the meta-analysis (N=8)

This diagram provides a clear visual representation of the meta-analysis process, highlighting the criteria for inclusion and exclusion of studies.
Table 1: Characteristics of studies included in the meta-analysis

| Study                  | Follow-up period (year) | Baseline mean age (year) | Number of PCa (events/participants) | OR (95% CI)     |
|------------------------|-------------------------|--------------------------|-------------------------------------|-----------------|
| (Rompay et al., 2019)  | 4.1                     | 70                       | 264/4571                            | 0.495 (0.431-0.568) |
| (Akaza et al., 2011)   | 4                       | 62.8                     | 5/54                                | 0.417 (0.135-1.295) |
| (Liang et al., 2012)   | 14                      | 72.6                     | 4/92                                | 0.766 (0.279-2.099) |
| (Azoulay et al., 2015) | 3                       | 72.1                     | 91/574                              | 0.885 (0.704-1.112) |
| (Roehrborn et al., 2011)| 4                       | 66                       | 79/3233                             | 0.616 (0.440-0.862) |
| (Ross et al., 2012)    | 5                       | 65                       | 8/47                                | 0.450 (0.206-0.985) |
| (Roehrborn et al., 2002)| 2                       | 66.3                     | 24/2167                             | 0.564 (0.341-0.935) |
| (Andriole et al., 2010)| 4                       | 63                       | 659/3305                            | 0.745 (0.664-0.836) |

Table 2: Weight of factors calculated based on a 4-point pairwise comparison scale

| Factor                     | Weight |
|----------------------------|--------|
| Information on medication  | 0.474  |
| Journal impact factor      | 0.286  |
| Sample size                | 0.169  |
| Level of evidence          | 0.072  |

All statistical analyses were performed using SAS software (ver. 9.4; SAS Institute, Cary, NC, USA). To take consideration of the numbers of events and sample sizes of the study groups, logistic regression can be applied for fixed-effect meta-analysis using the Logistic SAS procedure. Besides, we used the GLIMMIX SAS procedure for mixed-effects logistic regression in the random-effects meta-analysis.

RESULTS AND DISCUSSION

Results of the search

A total of 351 articles were identified (Figure 1). Duplicate articles, and those without dichotomous data, were excluded during the screening process. We also included papers in the reference sections of systematic reviews studying the relationship between the incidence of PCa and 5-ARI use (Andriole et al., 2010; Roehrborn et al., 2002).

In total, 37 papers passed the screening process, of which a further 29 were excluded according to the exclusion criteria outlined above. Therefore, a total of eight papers were included in the final meta-analysis.

Characteristics of the included studies

The characteristics of the eight studies included in the meta-analysis are shown in Table 1. We extracted data regarding the numbers of cases and non-cases in the intervention and control groups. The follow-up period ranged from 3 to 14 years, and the average age of participants ranged from 62.8 to 72.6 years (Akaza et al., 2011).

Evaluation of weights

We used the analytic hierarchy process (AHP) method to weight the studies (Benaim et al., 2010; de F.S.M. Russo and Camanho, 2015). Four weighting factors were used in this study: information regarding medications, impact factor (IF), sample size, and evidence level. We ranked these four factors based on a 4-point pairwise comparison scale. We calculated the weights of each factor using the AHP method (Table 2).

For each factor, studies were classified as high, high-intermediate, medium, low-intermediate, or low and were calculated weights of each study based on...
Table 3: Weight of studies by the weighting factors

| Study                        | Information on medication | Sample size | Level of evidence | Journal impact factor |
|------------------------------|----------------------------|-------------|-------------------|----------------------|
| (Rompay et al., 2019)        | 0.058                      | 0.333       | 0.066             | 0.067                |
| (Akaza et al., 2011)         | 0.181                      | 0.046       | 0.190             | 0.040                |
| (Liang et al., 2012)         | 0.181                      | 0.139       | 0.066             | 0.067                |
| (Azoulay et al., 2015)       | 0.058                      | 0.139       | 0.066             | 0.240                |
| (Roehrborn et al., 2011)     | 0.101                      | 0.078       | 0.190             | 0.240                |
| (Ross et al., 2012)          | 0.058                      | 0.046       | 0.041             | 0.067                |
| (Roehrborn et al., 2002)     | 0.181                      | 0.078       | 0.190             | 0.040                |
| (Andriole et al., 2010)      | 0.181                      | 0.139       | 0.190             | 0.240                |

Table 4: Final weight of each study

| Study                        | Weight |
|------------------------------|--------|
| Van Rompay MI (2019)         | 0.108  |
| Akaza H (2011)               | 0.119  |
| Liang J (2012)               | 0.133  |
| Azoulay L (2015)             | 0.124  |
| Roehrborn CG (2010)          | 0.143  |
| Ross AE (2012)               | 0.057  |
| Roehrborn CG (2002)          | 0.124  |
| Andriole GL (2010)           | 0.191  |

an 8-point scale pairwise comparison (Table 3).

Relatively high scores were assigned to studies with high independence of dutasteride among the variables. High scores were also given to trials using dutasteride alone, and low scores to those in which dutasteride was used in conjunction with finasteride, which has the same mechanism of action. High weights were given to studies with larger samples and higher IF values and evidence level (more reliable research method). The final weights were calculated by matrix multiplication of the weight of factors and weight of studies (Table 4).

Meta-analysis

The overall OR for both the fixed- and random-effects models was 0.669. The 95% CI of the random-effects model (0.526–0.851; $P = 0.0056$) was wider than that of the fixed-effect model (0.548–0.817; $P < 0.0001$) (Figure 2). The results suggested that dutasteride reduces the risk of PCA.

Conclusions

The results of this study showed that the incidence of PCA was significantly reduced when taking dutasteride alone. However, further studies exploring the side effects of dutasteride are required. Besides, additional studies are needed to verify the correlation between dutasteride and PCA risk.

Conflict of Interest

The authors declare that they have no conflict of interest.

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