Male Breast Cancer and 5α-Reductase Inhibitors Finasteride and Dutasteride

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Purpose: We examined the association between 5α-reductase inhibitors and male breast cancer.

Materials and Methods: Study participants were men 40 to 85 years old, with prescription and medical coverage, enrolled in the United States IMS LifeLink™ Health Plan claims database between 2001 and 2009. Cases required a primary breast cancer diagnosis (ICD-9-CM 175.x) on 2 different dates and a procedural code for mastectomy or lumpectomy/partial mastectomy with evidence of continuous care (radiation/chemotherapy or diagnoses in 2 or more months). Eligible controls were within 5 years in age and had duration of prior health care enrollment within 6 weeks. Risk set sampling selected 20 controls per case. We assessed the rate ratio for male breast cancer with 5α-reductase inhibitor exposure using conditional logistic regression. Analyses were stratified by duration of health care enrollment before diagnosis (1 year or more, 2 years or more and 3 years or more), each incremental 180 and 365 days of cumulative 5α-reductase inhibitor exposure, and period specific time frames before diagnosis (years 1, 2 and 3).

Results: We identified 339 breast cancer cases matched to 6,780 controls. No statistically significant associations were observed between 5α-reductase inhibitors and breast cancer regardless of exposure assessment before the index date (1 year or more—RR 0.70, 95% CI 0.34−1.45; 2 years or more—RR 0.59, 95% CI 0.24−1.48; or 3 years or more—RR 0.75, 95% CI 0.27−2.10). Each subsequent 180 days (RR 1.02, 95% CI 0.67−1.53) and 365 days (RR 1.03, 95% CI 0.45−2.37) of cumulative 5α-reductase inhibitor therapy and period specific rate ratios also showed null associations.

Conclusions: The lack of an association in our study suggests that the development of breast cancer should not influence the prescribing of 5α-reductase inhibitor therapy.

Key Words: breast neoplasms, male; 5-alpha reductase inhibitors

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor

FDA = Food and Drug Administration

PPV = positive predictive value

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THE 5α-reductase inhibitors finasteride and dutasteride are prescribed to men for the treatment of benign prostatic hyperplasia. These drugs act to prevent the conversion of testosterone to 5α-dihydrotestosterone, resulting in a reduction in androgen activity.[1] This can slow

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enlargement of the prostate,[2,3] reduce the potentiation of androgenic alopecia,[4] and may alter the risk of prostate and breast cancer.

Several studies have examined 5ARIs for chemopreventive effects. Two randomized clinical trials, the PCPT (Prostate Cancer Prevention Trial)[5] and the REDUCE (REduction by DUtasteride of prostate Cancer Events) trial,[6] were conducted to evaluate the effect of 5ARIs on the prevention of prostate cancer. Both trials demonstrated a significant chemoprotective effect of 5ARIs in the reduction of the cumulative prostate cancer incidence. However, an increased incidence of high grade prostate cancer was observed in both studies, leading the FDA to issue a drug safety communication to convey this information.[7]

It has been hypothesized that by increasing the estrogen-to-testosterone ratio, 5ARIs may also increase the risk of male breast cancer.[8,9] This idea is supported by 50 male breast cancer cases that have been reported with 5ARIs,[9] which fostered 5ARI label updates to include breast cancer case reports.[10] Therefore, in this study we examine the association between 5ARIs and male breast cancer.

MATERIALS AND METHODS

Data Source

The IMS LifeLink database contains paid claims from 102 health care plans in the United States. It contains fully adjudicated medical and pharmacy claims for more than 68 million patients, including inpatient and outpatient diagnoses and procedures (ICD-9-CM format) in addition to retail and mail-order prescription records. Compared to the United States Census, the data capture 16% of males age 35 to 44 years, 17% age 45 to 54 years, 13% age 55 to 64 years and 8% older than 65 years. Data on men older than 65 years are captured through Medicare Advantage, a privatized health care plan in which recipients pay to improve basic Medicare coverage, combining health care and prescription services with no gap in coverage to provide health care data that are generally more inclusive than general Medicare and Part D services. The LifeLink database is subject to quality checks to ensure data quality and minimize error rates.[11]

Cases and Controls

The study period was January 2001 to June 2011. Men 40 to 85 years old with a minimum of 1 year of prior health care enrollment as well as evidence of medical and prescription coverage were eligible for case and control selection. Cases required a primary breast cancer diagnosis (ICD-9-CM 175.x) on 2 different dates and a procedural code (CPT-4) for mastectomy or lumpectomy/partial mastectomy with evidence of continuous care (radiation/chemotherapy or diagnoses in 2 or more months). The index date was the first diagnostic or procedural breast cancer claim. This algorithm has a 93% PPV for incident breast cancer in women and 80% sensitivity compared to SEER (Surveillance, Epidemiology, and End Results) data.[12] As a sensitivity analysis, secondary ascertainment included all cases with diagnostic and surgical breast cancer claims. At the index date eligible controls were within 5 years in age and had duration of prior health care enrollment within 6 weeks. Risk set sampling selected 20 controls per case.

Exposure

We evaluated exposure to the 5ARI formulations finasteride (Proscar®) and dutasteride (Avodart®), which are both approved for the treatment of benign prostatic hyperplasia. Finasteride (Propecia®) was excluded from the study as a result of its low use, lower dose and different indication (androgenic alopecia). 5ARI exposure was assessed from initial health care enrollment until the index date. Matching on duration of prior enrollment ensured a similar exposure assessment time frame between cases and controls. Exposure assessment was broken down by length of assessment period, cumulative exposure and period specific exposure in the statistical analysis.

Statistical Analysis

Rate ratios and 95% CIs for breast cancer with 5ARI exposure were calculated using conditional logistic regression. Because the risk window for breast cancer after 5ARI exposure is unknown, stratified analyses were conducted to assess risk within specific induction time frames. In these stratified analyses cases and their matched controls were included only if they had health care enrollment during the entire exposure assessment window. Cases were matched by duration of prior health care enrollment to ensure that the 1:4 matching was preserved in all analyses.

The primary analysis was stratified by duration of health care enrollment before diagnosis (1 year or more, 2 years or more and 3 years or more). This stratification allows insight into the risk window (ie time frame) for assessment of the exposure-outcome association. Cases with a longer duration of prior health care enrollment have a longer documented time frame without breast cancer claims. Thus, these cases would be expected to have a higher PPV and a more accurate date of diagnosis, preventing a bias toward the null from a nondifferential outcome misclassification. This setup also allows evaluation for increased risk with a longer exposure assessment time frame, which could indicate increased breast cancer risk through cumulative exposure or time from initial exposure. Additional analysis was limited only to the assessment of finasteride.

A secondary analysis was conducted to assess breast cancer risk through cumulative 5ARI exposure. We created exposure covariates to assess risk with each incremental 180 days and 365 days of 5ARI exposure.

A tertiary analysis was used to evaluate period specific RRs stratified to assess risk within specific induction time frames (year 1—days 0 to 365, year 2—days 366 to 730 and year 3—days 731 to 1,095) before the index date. Isolating shorter time windows for exposure assessment results in decreased study power for each assessment. These analyses were intended to assess for a trend in the point estimate, whereby a trend toward an increased or decreased