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Use of 5α-reductase inhibitors for benign prostate hypertrophy and risk of high-grade prostate cancer: A French population-based study

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Structured abstract

Background – To assess the association between 5α-reductase inhibitor (5-ARI) use and high grade (Gleason score 8-10) prostate cancer.

Methods – We set up a population-based nested matched case-control study using the French Health Insurance Database linked to data from all Brittany (France) path labs. Among 74,596 men with ≥ 1 drug reimbursement for symptomatic benign prostate hypertrophy

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between January 1, 2010 through December 31, 2011, 767 incident prostate cancer cases between January 1, 2012 through December 31, 2013 were matched on age and delay between the first observed delivery of drug for benign prostate hypertrophy (5-ARI, alpha-blockers or phytotherapy) and diagnostic date of the case to five controls, using an incidence density sampling design.

Results - 963 men (153 cases, 810 controls) had been exposed to 5-alpha reductase inhibitors. A statistically significant heterogeneity ($p = 0.0048$) was detected across cancer grades when estimating association between prostate cancer and 5-alpha reductase inhibitors long term use ($\geq$ 2 years) versus no 5-alpha reductase inhibitor exposure: adjusted conditional odds ratio was 1.76 [0.97-3.21] for Gleason $\geq$ 8, and 0.64 [0.44-0.93] for Gleason < 8.

Interpretation - Our results supported an increased risk for high-grade and a decreased risk for low-grade prostate cancer. Patients treated for longer than 2 years with 5-alpha reductase inhibitors should be informed of increased risk for the development of high-grade disease.

ClinicalTrials.gov identifier: NCT02873117.

Abbreviations

5-ARI: 5-alpha-reductase inhibitors

BPH: benign prostate hypertrophy

ICD-10 codes: International Classification of Diseases, 10th edition

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LTD: long-term disease

OR: odds ratio

PCPT: Prostate Cancer Prevention Trial

PSA: prostate specific antigen

REDUCE: Reduction by Dutasteride of Prostate Cancer Events

RR: risk ratio

Introduction

With a high prevalence(1), a risk of morbidity from treatment(2) or from active surveillance with follow-up biopsies(3), primary prevention of prostate cancer is attractive. Two large randomized trials(4,5) have demonstrated that 5-alpha-reductase inhibitors (5-ARI) reduced overall prostate cancer risk by 20% to 25%, but they also reported a statistically significant increased risk of high-grade cancer (Gleason scores 7-10) and so far the use of 5-ARI is not recommended for primary prevention(6–8). Reason for the observed increased risk is controversial(9) including false result through detection bias(10,11).

Treatment with 5-ARI has clear benefits for men with lower urinary tract symptoms related to benign prostate hypertrophy(12,13). In those men, no difference was observed regarding the number of Gleason score 8-10 cancers in men allocated to dutasteride compared to those allocated to tamsulosin(14). Though three observational studies(15–17) reported somehow reassuring results, these findings did not rule out an increased risk of high-grade prostate cancer. Considering that the association between 5-ARI use and high-grade prostate cancer is still debated, we set up the CANARI study investigating the association

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between 5-ARI use and prostate cancer according to Gleason score (< 8 or ≥ 8), compared to 5-ARI non-users.

Patients and Methods

Study design, setting and participants. This population-based matched case-control study used data (2010 to 2013) from the comprehensive French Health Insurance Data (SNIIRAM) linked to data from all path labs located in Brittany, France.

Design description and linkage methodology were reported elsewhere(18). Among men living in Brittany, all treated for symptomatic or complicated BPH in 2010-2011 (Supplementary Table S1), we identified incident cases of prostate cancer in 2012-2013 (Supplementary Table S2) and confirmed the diagnosis by linkage to pathology results (Gleason score). We then defined: men with high-grade prostate cancer (Gleason score ≥ 8) and men with low-grade prostate cancer (Gleason score < 8). To be eligible, a case had to have a delay of at least one year between the first observed delivery of drug for BPH and prostate cancer diagnosis. Figure 1 displays a flowchart. For each case, five controls alive and free of prostate cancer at diagnosis date of the case (index date) were randomly selected from the cohort. They were matched on age and delay between the first observed delivery of drug for BPH and index date through an incidence density sampling design.

Exposure. We defined "5-ARI users" as patients having at least two deliveries; the others were categorized as "5-ARI non-users" (Supplementary Table S1). Exposure was quantified by the cumulative duration of 5-ARI dispensed calculated from all data observed (backward from index date to January 1st, 2010) and categorized for sake of clarity into three classes (less than 1 year, [1-2[and ≥ 2 years).

Variables and sources of data. Using SNIIRAM data(19), we classified cases and controls as having or not some pre-specified comorbidities (Supplementary Table S2). We also obtained dates of performed transurethral resections, prostate biopsy procedures, and PSA measurements (results unavailable). On the 2010-2013 period, French guidelines as regards prostate biopsies were the same as European guidelines which recommend 10 to 12 biopsy cores but nor more 12 (20,21). In Brittany pathology laboratories, 12 biopsy cores are usually sent for analysis.

Study size. At a 5% two-sided significance level, upon the hypothesis of 5-ARI exposure frequency of 20% among controls(22), 98 cases of high grade prostate cancer and 490 controls (1:5 case-to-control ratio) allowed to detect an odds ratio of 2.0 with 80% power, keeping in mind that matching improves power though in an unknown manner.

Statistical methods. Characteristics of patients were described according to their case-control status. Measure of association used odds ratio (and 95% confidence interval) through conditional logistic regression to take into account matching. Multivariate conditional logistic regression analysis was performed to further adjust on potential risk factors. As PSA measurement and number of prostate samples (biopsy or transurethral resection) were potentially in the causal pathway leading to prostate cancer, a sensitivity analysis without adjustment on those parameters was also made.

Association between prostate cancer and 5-ARI exposure was expected to be different whenever low-grade or high-grade cancer was considered. An interaction term between exposure and prostate cancer grade was introduced in the logistic model in order to allow different association strength according to the considered individual outcome (low or high-grade prostate cancer) and to test homogeneity across these individual components of the

composite outcome(23). A sensitivity analysis was made according to the recently proposed new five-tiered Gleason grade groups (GGGs)(24).

Statistical analyses used the LOGISTIC procedure of the SAS software version 9.4 (SAS Institute Inc, Cary, NC) with a STRATA statement.

Ethical considerations. The study got regulatory approval (CNIL: DR-2014-084); ClinicalTrials.gov identifier: NCT02873117.

Results

Participants. Among 74,596 eligible men, 859 cases of confirmed prostate cancer were identified in 2012-2013 (Figure 1); 767 cases (including 153 "5-ARI users") were available for the analysis, matched to 3835 controls (including 810 "5-ARI users").

Descriptive data. After matching, mean age was 69.3 years, and men with Gleason scores < 8 were younger than those with Gleason ≥ 8 (mean age 68.2 versus 76.0 years) (table 1). All cases had at least one prostate sample before the index date compared to 10.6 % in controls. Cases had more frequently more than one PSA measurement than in controls (96.5 % vs. 82.4 %). Excluding the biopsy which made the diagnosis, 71.9 % of cases and 3.7 % of matched controls had at least 1 one another biopsy before diagnosis; 25.4 % of cases and 6.7 % of matched controls had TURP. Cases and controls were not markedly different as regards measured co-morbidities.

Exposure data. 153 (20.0 %) cases and 810 (21.1%) controls were "5-ARI users" before index date and 400 men had a duration of use of 5-ARI ≥ 2 years: 58 were cases (including 38 with Gleason < 8 and 20 with Gleason ≥ 8) and 342 were controls (Supplementary Table S3). When comparing "5-ARI users" to "5-ARI non-users", no substantial differences were observed, including PSA measurement and prostate samples (table 2). Most of "5-ARI non-

users" received alpha-adrenoreceptor antagonists (Tamsulosin, 35 %; Alfuzosin, 24 %), but also *Serenoas repens* (22 %) and *Pygeum africanum* (11 %).

***Main results*.** Matched unadjusted estimates and confounder-adjusted estimates are shown in Figure 2 and Supplementary Table S3. Conditional adjusted odds ratios for low-grade and high-grade prostate cancer were, respectively 0.80 [0.64-1.01] and 1.21 [0.74-1.98] for "5-ARI users" compared to "5-ARI non-users". As regard long term users (≥ 2 years), a statistically significant heterogeneity (p = 0.0048) was detected between prostate cancer grades: adjusted conditional odds ratio was 1.76 [0.97-3.21] for Gleason ≥ 8, and 0.65 [0.45-0.93] for Gleason < 8. A sensitivity analysis using new Gleason grading system showed similar results (Supplementary Table S4).

Discussion

In our study targeting subjects receiving drugs licensed for symptomatic or complicated benign prostate hypertrophy, a qualitative significant heterogeneity was observed across cancer grades when estimating association between prostate cancer and 5-ARI long term use (≥ 2 years) versus no 5-ARI exposure.

Our study results differ in some important aspects of clinical setting and methodology to other observational studies(15–17) but appear in line with PCPT and REDUCE trials(4,5). Our clinical setting was more similar to the CombAT trial(14) than PCPT(4) and REDUCE trials(5). In a Finnish cohort study, risk of cancer with scores 7-10 was non-significantly increased in finasteride users compared to non-users(15). A Swedish population-based case-control study reported that an increasing duration of exposure to 5-ARI was associated with a decreased risk of Gleason scores 2-6 and 7; no significant association in risk of Gleason scores 8-10 was observed with increasing exposure time(16). Lastly, another Swedish

population-based cohort study(17) reported that 5-ARI decreased the risk for prostate cancer with Gleason scores 6 and 7, and that 5-ARI did not statistically significantly affect the long-term risk of prostate cancer with Gleason scores 8-10 over a 8-year period compared to men not taking 5-ARI; more in depth, a statistically increased risk after less than 2 years of exposure to 5-ARI (HR = 1.56), became not statistically significant (HR = 1.25) with a further adjustment on PSA before treatment and there was no increased risk thereafter: authors explained that these early detected high-grade cancers were likely potential prevalent cancers, more easily diagnosed by prostate shrinkage. Of note, a one-year delay has been used to remove prevalent cancers detected due to the initial PSA test(17). Furthermore, a transient early increased risk for cancer could be related a true effect of 5-ARI selecting susceptible clones; previous studies showed no specific prostatic histologic modification in finasteride treated patients and suggested that high-grade prostate cancer could be due to the cell capacity to survive in a maybe less hormonally sensitive environment(25,26). These three observational studies used men free of prostate cancer as controls(16), compared drug users to non-users(15), or used "non 5-ARI users" as reference(17) (no details as regards BPH status or non 5-ARI BPH treatment were provided). Interestingly, Murtola's and Robinson's studies also assessed the association between exposure to alpha-adrenoreceptor antagonists and prostate cancer: men using alpha-adrenoreceptor antagonists had either an increased (16) or a non-significant (15) risk of low-grade prostate cancer. This result was thought to be related to a detection bias considering that men with lower urinary tract symptoms have a higher seeking of prostate cancer. Even in PCPT trial, a detection bias was put forward to explain the observed higher proportion of high-grade cancers in 5-ARI users; indeed 5-ARI decreased prostate volume (plus tumor shrinkage) and increased sensitivity of PSA. The last reassuring factor is that there is no

increased mortality rate among long-term 5-ARI users(27). Our study design did not allow to assess overall survival. Whatever, having been diagnosed with high grade prostate cancer is associated with stress and the need for treatment although the drug was initially given for a benign disease.

Our study has some strengths. First, we used a population-based nested matched case-control design which minimizes selection bias(28). Selection of eligible subjects for cohort entry was made through drug claims which were collected timely and prospectively; hence recall bias does not apply and misclassification on exposure is minimized and at least non-differential. Second, comparing treated patients, we selected subjects seeking a medical attention for symptoms justifying a drug prescription. We thought minimizing confounding by indication, compared to previous studies which used non-treated patients(4,5,15–17) as reference. Third, we thought detection bias was minimized; as PSA measurement and prostate sampling are potentially in the causal pathway leading to prostate cancer; even though no PSA results were available, the recurrence of PSA dosage and the use of prostate sampling were proxies of prostate cancer exploration; thus, we conducted a sensitivity analysis without adjustment on those parameters, showing similar results to the main analysis with full-adjustment. Fourth, we set up a two-year restriction period during which subjects had to remain free of prostate cancer diagnosis to be eligible for inclusion, reassuring us that cases were truly incident prostate cancer cases. Fifth, we had no attrition bias. Some weaknesses have to be also discussed: representativeness is more debatable than would have been a nationwide study but linkage to pathology labs imposed a restricted area. We had no information on prostate volume and body mass index but a previous study showed that such an adjustment did not materially affect the results(15). Other studies suggested that prostate volume was not related to prostate cancer risk(29) and could not be

predictive of histological grade(30). We did not have information on dietary patterns but when comparing drug users between each other such healthy-user effect is thought to be less problematic. We had no valid information on family cancer status or highest level of education attained, but such an adjustment did not seem to change the results in a previous study(16). Lastly, there is a potential for exposure misclassification as regards short or mid-term users (< 2 years) because we had no claims data before 2010; on the other hand, we are confident in long-term users (≥ 2 years) classification whenever observed.

The so-far rather re-assuring message as regards high-grade prostate cancer should be switched to more cautious information. Notwithstanding clear clinical benefits of 5-ARI, we should consider any substantial increased risk of high-grade cancer (worse prognosis) when choosing between therapies for symptomatic or complicated BPH. Patients treated for longer than 2 years with 5-alpha reductase inhibitors should be informed of increased risk for the development of high-grade disease.

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Legends

Figure 1: Flow chart.

Figure 2. Conditional adjusted odds ratios for prostate cancer.

Matching on age and delay between the first observed delivery of drug for BPH and index date through an incidence density sampling design with further adjustment on diabetes, lowering-lipid drug claims, obesity, COPD, annual number of prostate sample collection(s) (i.e., biopsy or transurethral resection) before the sample which allowed the diagnosis of cancer for cases) and annual number of PSA measurement.

p-value for heterogeneity across cancer grades (high-grade and low-grade) when estimating association between prostate cancer and 5-ARI long term use ($\geq$ 2 years) versus no 5-ARI exposure (reference) = 0.0048.

Table 1. Characteristics of cases (prostate cancer) and matched controls.

SD denotes standard deviation; data are number (%) of individuals unless stated otherwise.

COPD denotes chronic obstructive pulmonary disease.

(a) before index date and the date of sample which allowed the diagnosis of cancer for cases.

(b) number of prostate sample collection(s), i.e. biopsy or transurethral resection, before index date and the date of the sample which allowed the diagnosis of cancer for cases.

Table 2. Subjects' characteristics according to drug exposure.

(a) before index date and the date of the sample which allowed the diagnosis of cancer for cases.

(b) number of prostate sample collection(s), i.e. biopsy or transurethral resection, before index date and the date of the sample which allowed the diagnosis of cancer for cases.

Supplementary Table S1: ATC classification codes.

Supplementary Table S2: Definition of variables**.**

Supplementary Table S3: Risk of prostate cancer diagnosis.

Supplementary Table S4: Sensitivity analysis using new Gleason grading system.

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Table 1 *Characteristics of cases (prostate cancer) and matched controls*

	Overall		Gleason score of cancer			
			< 8		≥ 8	
	Cases	Controls	Cases	Controls	Cases	Controls
	N = 767	N = 3 835	N = 662	N = 3310	N = 105	N = 525
Age (years), mean (SD)	69.3 (8.6)	69.3 (8.6)	68.2 (8.1)	68.2 (8.1)	76.0 (8.5)	76.0 (8.5)
PSA measurement [a], n (%)						
None	27 (3.5)	676 (17.6)	16 (2.4)	545 (16.5)	11 (10.5)	131 (25.0)
1-2	236 (30.8)	1764 (46.0)	191 (28.9)	1560 (47.1)	45 (42.9)	204 (39.9)
≥ 3	552 (72.0)	1395 (36.4)	455 (86.4)	1205 (62.5)	49 (46.7)	190 (36.2)
All prostate samples [a], n (%)	767 (100)	407 (10.6)	662 (100)	357 (10.8)	105 (100)	50 (9.5)
Previous prostate biopsy [b], n (%)						
None	139 (18.1)	3693 (96.3)	124 (18.8)	3183 (96.2)	15 (14.3)	510 (97.1)
1 biopsy	562 (73.3)	128 (3.3)	478 (72.2)	114 (3.4)	84 (80.0)	14 (2.7)
2 biopsies	55 (7.2)	14 (0.4)	51 (7.7)	13 (0.4)	4 (3.8)	1 (0.2)
≥ 3 biopsies	11 (1.4)	0	9 (1.4)	0	2 (1.9)	0
Transurethral resection, n (%)	195 (25.4)	256 (6.7)	163 (24.6)	219 (6.6)	32 (30.5)	37 (7.0)
COPD, n (%)	26 (3.4)	169 (4.4)	22 (3.3)	140 (4.2)	4 (3.8)	29 (5.5)
Diabetes mellitus, n (%)	91 (11.9)	532 (13.9)	69 (10.4)	454 (13.7)	22 (21.0)	78 (14.9)
Lipid-lowering drug claims, n (%)	382 (49.8)	1994 (52.0)	324 (48.9)	1704 (51.5)	58 (55.2)	290 (55.2)
Obesity, n (%)	38 (4.9)	132 (3.4)	31 (4.7)	118 (3.6)	7 (6.7)	14 (2.7)

SD denotes standard deviation; data are number (%) of individuals unless stated otherwise.

COPD denotes chronic obstructive pulmonary disease.

(a) before index date and the date of sample which allowed the diagnosis of cancer for cases.

(b) number of prostate sample collection(s), i.e. biopsy or transurethral resection, before index date and the date of the sample which allowed the diagnosis of cancer for cases.

Table 2 *Subjects' characteristics according to drug exposure*

	5-ARI users N = 963	5-ARI non-users N = 3639
Age (years), mean (SD)	71.7 (8.5)	68.6 (8.5)
PSA measurement [a]		
None	141 (14.6)	562 (15.4)
1-2	396 (41.1)	1604 (44.1)
≥ 3	426 (44.3)	1473 (40.5)
Previous prostate samples [b]		
None	827 (85.9)	3211 (88.2)
1 sample	127 (13.2)	380 (10.4)
2 samples	9 (0.9)	45 (1.2)
≥ 3 samples	0	3 (0.1)
COPD	41 (4.3)	154 (4.2)
Diabetes mellitus	125 (13.0)	498 (13.7)
Lipid-lowering drug claims	530 (55.0)	1846 (50.7)
Obesity	35 (3.6)	135 (3.7)

(a) before index date and the date of the sample which allowed the diagnosis of cancer for cases.

(b) number of prostate sample collection(s), i.e. biopsy or transurethral resection, before index date and the date of the sample which allowed the diagnosis of cancer for cases.
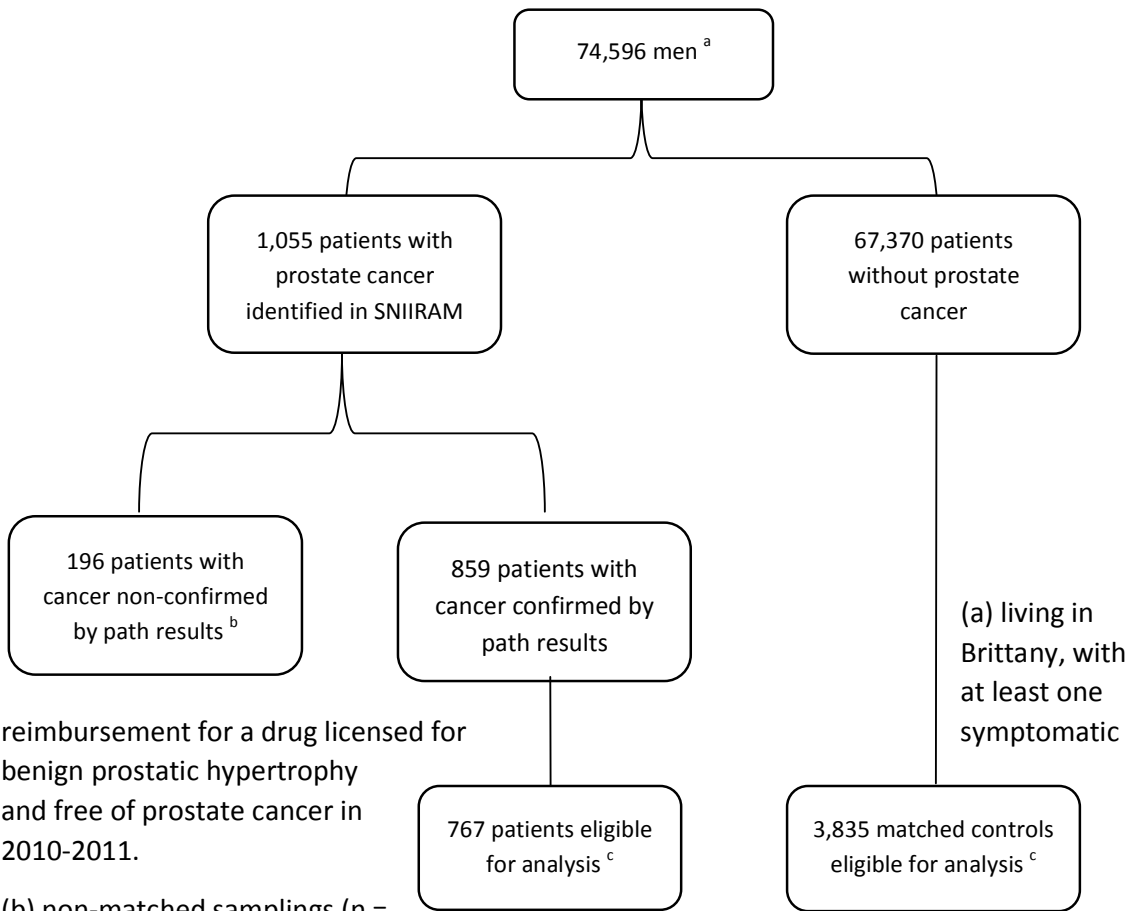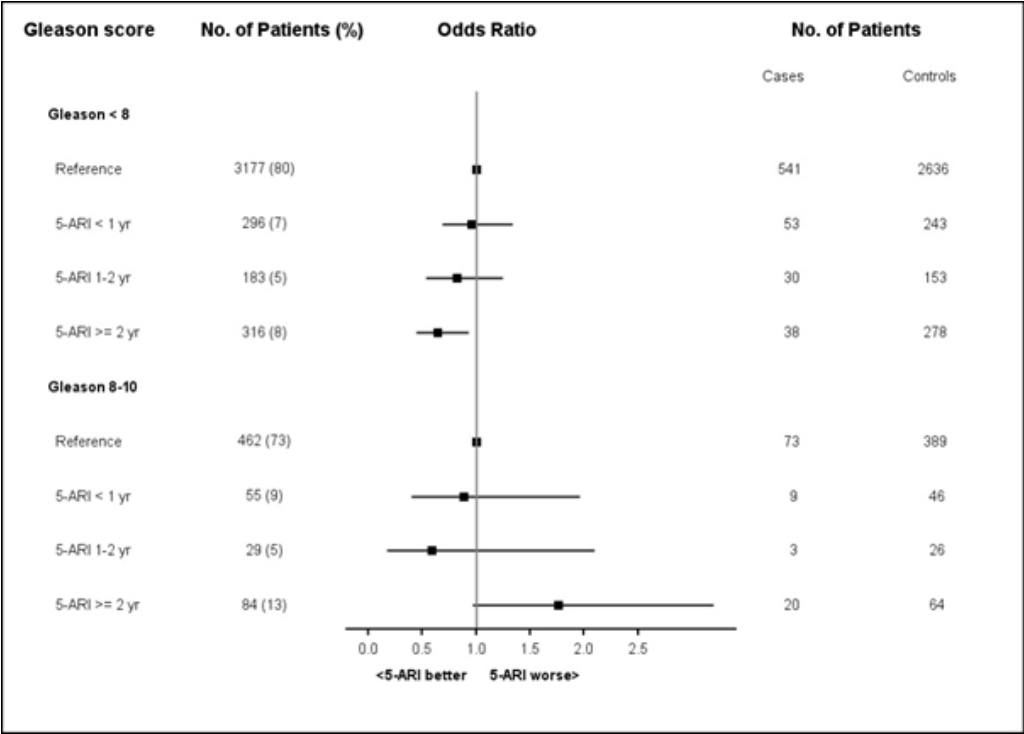
Figure 1. Flow chart.

74,596 men [a]

1,055 patients with prostate cancer identified in SNIIRAM

67,370 patients without prostate cancer

196 patients with cancer non-confirmed by path results [b]

859 patients with cancer confirmed by path results

(a) living in Brittany, with at least one symptomatic

reimbursement for a drug licensed for benign prostatic hypertrophy and free of prostate cancer in 2010-2011.

767 patients eligible for analysis [c]

3,835 matched controls eligible for analysis [c]

(b) non-matched samplings (n = 122 patients), inadequate matching (n = 28 patients) and 46 patients with matched sampling but without any positive examination results (Gleason score).

(c) Patients initiating treatment for symptomatic or complicated benign prostate hypertrophy within a year before index date were not eligible for the analysis.

Figure 2. Conditional adjusted odds ratios for prostate cancer.

Matching on age and delay between the first observed delivery of drug for BPH and index date through an incidence density sampling design with further adjustment on diabetes, lowering-lipid drug claims, obesity, COPD, annual number of prostate sample collection(s) (i.e., biopsy or transurethral resection) before the sample which allowed the diagnosis of cancer for cases) and annual number of PSA measurement.

p-value for heterogeneity across cancer grades (high-grade and low-grade) when estimating association between prostate cancer and 5-ARI long term use (≥ 2 years) versus no 5-ARI exposure (reference) = 0.0048.