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Male hormone-interfering drugs and meningioma development

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Abstract

Background. Extremely strong associations between male hormone-interfering drugs and meningiomas have been reported in two previous studies, but these findings are limited by small size of the study populations and possibly by surveillance- and selection bias. Thus, such possible and indeed very interesting association must be investigated in a large, unselected cohort. Accordingly, the aim of this study was to determine whether patients exposed to male hormone-interfering drugs had a higher risk of meningioma development in a nationwide cohort study.

Methods. A retrospective Danish nationwide cohort study with follow-up from January 1, 1996 to December 31, 2016. Exposure was use of male hormone-interfering drugs (5-α-reductase-inhibitors, luteinizing hormone-releasing hormone agonist, steroidal antiandrogen, and nonsteroidal antiandrogen). Hazard ratio of first-time diagnosis of meningioma according to drug use was estimated using Cox proportional hazards model with adjustment for age and birth year.

Results. The cohort included 244,696 men of which 64,047 had used male hormone-interfering drugs. Overall 444 meningiomas occurred during follow-up. No significant association was observed between use of male hormone-interfering drugs and the occurrence of meningioma (hazard ratio 1.02, 95% confidence interval 0.82–1.27). Similar results were observed 0–1, 2–4, and 5+ years after first use. In explorative analyses, no elevated risk association was observed for specific drugs (5-α-reductase-inhibitors, luteinizing hormone-releasing hormone agonist, steroidal antiandrogen, and nonsteroidal antiandrogen).

Conclusion. As opposed to previous studies, we found no evidence of an increased risk of meningioma in men treated with male hormone-interfering drugs.

Key Points

- Male hormone-interfering drugs were not associated with an increased risk of meningioma.
- No elevated risk of meningioma was observed for the specific subtypes of drugs.
- Similar results were observed 0–1, 2–4, and 5+ years after first use.

Meningiomas (WHO grades I–III) are the most commonly diagnosed primary intracranial tumor[1] with an incidence of 2–7/100.000/year for women and 1–5/100.000/year for men.[2] They originate from arachnoid cap cells and may require surgical resection if the lesion is symptomatic and surgically accessible. Two previous studies, with different types of populations and design, have found highly increased risks of meningioma development in patients treated with high-dose steroidal

Importance of the Study

Meningiomas have been suggested to occur in excess in patients treated with male hormone-interfering drugs in two studies (relative risk [RR] 11.4 [95% CI: 4.3–30.8], and odds ratio [OR] 3.28 [95% CI: 1.01–10.64], respectively). These drugs are used in management of prostate hyperplasia or—cancer, and if such association exist, it would affect millions of men worldwide. The aim of this study was to investigate the potential association between the use of male hormone-interfering drugs and meningiomas in an unselected large cohort without surveillance bias. This nationwide, register-based study included 244,696 men with prostate hyperplasia or—cancer, of which 64,047 used male hormone-interfering drugs. As opposed to the previous studies, we found no evidence of an increased risk of meningioma in men treated with male hormone-interfering drugs, even 5+ years after first use. In explorative analyses, no elevated associated risk was observed for specific drugs.

antiandrogens (SAA), such as Cyproterone Acetate (relative risk [RR] 11.4 [95% CI: 4.3–30.8] and odds ratio [OR] 3.28 [95% CI: 1.01–10.64], respectively).[3,4] Some case-reports have described meningiomas among male-to-female transsexual patients.[5–7] Some of the meningiomas have been observed to either stop their growth or shrink in size after discontinuing of Cyproterone Acetate (SAA).[5,7]

One study did not find an association between the use of luteinizing hormone-releasing hormone (LHRH) or antiandrogens and the risk of meningiomas (OR 0.33 [95% CI: 0.07–1.66] and OR 3.82 [95% CI: 0.42–34.94], respectively).[8] Male hormone-interfering drugs are widely used in the treatment of prostate hyperplasia- and carcinoma, the latter being the second most frequent cancer among men in the world.[9,10]Therefore, if the findings suggested by the aforementioned studies are true, it could have an impact on a large number of men worldwide. However, these two studies are limited by small size of the study populations and possibly by surveillance- and selection bias. To overcome these limitations, this potential and indeed very interesting association must be investigated in a large, unselected cohort.

The unique Danish registers allows investigation of the potential association between male hormone-interfering drugs and the occurrence of meningiomas in a large unselected cohort with long-term follow-up and minimal selection- and surveillance bias.

Material and Methods

Data Sources

The following registers were used: The Civil Registration System (CRS) has existed since 1968 and is continuously updated regarding demographic information.[11] Each individual in Denmark is given a social security number (CPR-number) that allows interlacement of the different registers. The National Patient Register (NPR) has registered all hospital admittances since 1977; furthermore, since 1995 also emergency room visits and outpatient contacts, registered by the International Classification of Diseases (ICD-8 and ICD-10).[12] The Danish Cancer Register (DCR) contains ICD-7 and ICD-10 as well as histologic diagnoses of all types of cancer as defined in the WHO classification systems. The National Prescription Register (NaPR) contains information on all subscribed medicine in Denmark since 1995, according to the Anatomical Therapeutic Chemical Classification System (ATC codes),[13] including information on date of dispensation, amount, and strength of the medicine.

Cohort

The main cohort consisted of all men living in Denmark, age 50 years or more, diagnosed with either prostatic hyperplasia (ICD-8: 60000, 60001, 60008, 60009, and ICD-10: DN40) or prostate carcinoma (ICD-8: 18599 and ICD-10: D61). Members of the cohort were identified by CPR-number using CRS[11] and NPR.[12] Exclusion criteria were preexisting meningioma or neurofibromatosis type 2 diagnosis (ICD-10: DQ850) at start of follow-up, see Figure 1 in Supplementary Material.

Exposure: Male Hormone-Interfering Drugs

Use of male hormone-interfering drugs was determined using the NaPR.[13] Male hormone-interfering drug use were identified by the ATC codes: G03HA (SAA), G04CB (5-α-reductase-inhibitors [5αRI]), L02AE (luteinizing hormone releasing hormone agonist [LHRH-agonist]), and L02BB (nonsteroidal antiandrogen [NSAA]).

Outcome: Meningioma

By using DCR and NPR, all first-time meningioma were identified using ICD7: 193.2, 223, ICD-8: 19219, 22500, 22501, 22502, 22503, 22507, 22509, 22520, 22521, 22522, 22523, 22524, 22525, 22528, 22529, 22599, 23839 and ICD-10: DD320, DD321, DD329, DC700, DC701, DC709.[12] The ICD-8 and ICD-10 codes were automatically reported to The National Patient Register. The diagnosis of meningioma was based on diagnoses given by specialized medical doctors of neurology, oncology, or neurosurgery. Surgical cases would also have a histological diagnosis (WHO

criteria) in the DCR. The same search was performed in the both registers to insure all cases of meningioma were identified.

Statistical Analyses

The individuals of the cohort were followed from January 1, 1996, their 50th birthday or the day of inclusion of prostate diagnosis, whichever was last, until one of the following events occurred: (a) diagnosis of a meningioma, (b) death, (c) emigration, (d) classified as missing person in CRS, (e) diagnosis of neurofibromatosis type II or (f) end of follow-up December 31, 2016. In all analyses, use of male hormone-interfering drug was treated as a time-dependent variable, such that cohort members are categorized as users after date of first redemption. For the main analysis a Cox-regression model with age as the underlying time scale and with the baseline hazard stratified by birth year was used to estimate the hazard ratio (HR) of meningioma development according to use of male hormone-interfering drug. The proportional hazards assumption of the main analysis was evaluated using a test for homogeneity of the HR in the age-intervals; 50–59, 60–69, 70–79, 80–89, and more than 90 years of age. We analyzed if the HR of meningioma depended on time since first use of male hormone-interfering drug (in intervals 0–1, 2–4, and 5 or more years of use, respectively). We estimated the HR of each of the male hormone-interfering drugs by limiting use to be defined by first the specific drug group and second the specific drug.

Furthermore, we restricted the cohort to include only those who had a prostate carcinoma or prostatic hyperplasia, respectively. Lastly, in a supplementary analysis among all men above 50 years of age we estimated age-adjusted HRs of meningiomas of combined effects of prostate diagnosis and male-hormone interfering drug use. In this analysis, both prostate diagnosis and MHID use were treated as time-varying exposures. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

Ethics Statement

The study has been approved by the Danish Data Protection Agency, no. 2015-57-0102. Danish law does not require ethical approval for register-based studies in Denmark.

Results

The cohort consisted of 244,696 patients. Of these 64,047 had used male hormone-interfering drugs by the end of follow-up (26.2%). The individual follow-up time varied from 1 day to 7,670 days with a median of 2,122 days. The risk time for never users was 1.351 million years and 0.378 million years for users. In the cohort, 444 patients were diagnosed with meningioma, consisting of 105 persons among users and 339 among never users. The mean age at which the patients were diagnosed with prostate disease was 69.9 and for their meningioma diagnosis they were 75.6 years of age. Regarding drug use, Finasteride and Dutasteride, with 45,948 and 15,429 users, respectively, were the most prevalent drug types. The HRs of meningioma in patients diagnosed with prostatic hyperplasia and prostate carcinoma, according to ever use and time since first use of male hormone-interfering drugs are shown in Table 1. Users did not have an increased risk when compared to never users. No users with 0–1 years, 2–4 years or 5 or more years since first use, respectively, had an elevated rate of meningioma compared to never users (Table 1). HRs in the age intervals 50–59, 60–69, 70–79, 80–89, and more than 90 years of age were similar (P = .87, data not shown).

The HR of meningioma according to different types of male hormone-interfering drugs are presented in Table 2. There were no significant increased rates related to specific types of drugs.

In two analyses using only diagnosis of either prostate carcinoma or prostatic hyperplasia as inclusion criteria, users had a HR 1.03 (95 % CI: 0.65–1.62) and 1.10 (95 % CI: 0.87–1.40), respectively compared to never users.

The analysis investigating combined effects of prostate diagnosis and MHID use is shown in Table 3. Here, it is shown that among men not treated with male-hormone interfering drugs the risk of meningioma was higher 1.78 (95 % CI: 1.57–2.01) if they had a prostate diagnosis.

Discussion

In this large unselected nationwide cohort study of prostate patients, we investigated the risk of meningioma associated with overall use of male hormone-interfering

Table 1. Hazard ratio (HR) of meningioma in patients diagnosed with prostatic hyperplasia and prostate carcinoma, according to the use-, and time since first use of male hormone-interfering drugs compared to never users

Time since first use	Risk time (person-years)	Meningioma cases	HR	95 % CI
Never use	1,351,000	339	1	Reference
Ever use	378,000	105	1.02	(0.82–1.27)
0–1 years	76,000	19	0.97	(0.61–1.55)
2–4 years	103,000	27	1.01	(0.68–1.50)
5+ years	199,000	59	1.04	(0.79–1.39)

CI, confidence interval; HR, hazard ratio.

Table 2. Hazard ratio (HR) of meningioma in patients with prostatic hyperplasia and prostate carcinoma, according to ever use of different types of male hormone-interfering drugs, compared to never users

Types of male-hormone interfering drugs	Risk time (person-years)*	Number of meningiomas*	HR†	(95% CI‡)
5-α-Reductase-inhibitors	359,428	99	1.01	(0.80–1.26)
Finasteride	299,454	77	0.94	(0.74–1.21)
Dutasteride	78,576	30	1.30	(0.89–1.91)
LHRH-agonist	5,109	<5§	1.63	(0.40–6.53)
Buserelin	254	0	—	
Leuprorelin	741	0	—	
Goserelin	3,953	<5§	2.05	(0.51–8.21)
Triptorelin	256	0	—	
Steroidal antiandrogens				
Cyproterone	6,141	<5§	1.81	(0.58–5.64)
Nonsteroidal antiandrogen	15,751	6	1.43	(0.64–3.21)
Flutamide	6,548	0	—	
Bicalutamide	9,887	6	2.16	(0.97–4.85)
Enzalutamide	1	0	—	
Nilutamide	9	0	—	

*Some patients were exposed to more than one type of drug, therefore the total numbers do not add.
†HR, hazard ratio.
‡CI, confidence interval.
§Due to Danish law it is not permitted to specify counts less than 5.

Table 3. Age-adjusted hazard ratios (HRs) of meningiomas of combined effects of prostate diagnosis and male-hormone interfering drug use

	HR*	(95% CI†)
Background population controls not treated with MHID‡	1.00 (Ref)	
Hospital diagnosis of prostate disease not treated with MHID	1.78	(1.57–2.01)
Hospital diagnosis of prostate disease treated with MHID	1.75	(1.43–2.15)

*HR, hazard ratio.
†CI, confidence interval.
‡Male-hormone interfering drugs.

drugs as well as the risks associated with use of the individual subtypes: SAA, 5αRI, LHRH-agonist, and NSAA. No evidence was found of an increased short- or long-term risk of meningioma in men treated with male hormone-interfering drugs, overall (HR: 1.02, 95 % CI: 0.82–1.27) or within subtypes. This is to our knowledge the first large scale population-based cohort study investigating this important research question of relevance for all users of male hormone-interfering drugs.

Only the three aforementioned studies have previously investigated the association between use of male hormone-interfering drugs and risk of meningiomas.[3,4] The first was a Spanish retrospective cohort study, performed in a Spanish primary care database (BIFAP),[3] which showed a highly increased rate ratio (RR: 11.4, 95% CI: 4.3–30.8) of meningioma among 2,474 users of high-dose SAA as compared to never users.

The other study, a retrospective cohort study with a nested case–control analysis, was conducted using individuals identified from The Health Improvement Network (THIN) UK primary care database.[4] This study involved 196 meningioma patients and 2,653 controls. The result of this study showed an OR of 3.28 (95% CI: 1.01–10.64) for users of SAAs compared to never users.[4]

The two studies were both limited to only four exposed cases of meningiomas and the higher risk among users reported in these studies may be because users were compared to the general population.[4] Thus, there might have been an increased tendency to refer the patients in the exposed group in the second study to brain imaging studies, because of their active cancer diagnosis, resulting in surveillance bias.

The analysis investigating combined effects of prostate diagnosis and MHID use shows that men with prostate

diagnosis have higher incidence of meningioma than men without diagnosis. This most likely reflect the well-known surveillance bias that arises due to a higher level of awareness of symptoms in patients with regular contacts to the health care system. A causal relation between prostate disease and meningiomas is less likely as systemic baseline hormone levels to our knowledge are not different between men with prostate cancer and controls. This is supported by the review by Burton et al.[14]: "a pooled analysis of 18 pooled prospective observational studies has not shown circulating androgen levels to be associated with risk of prostate cancer." It is also points to the fact that the development of prostate cancer is more influenced by the level of intraprostatic conversion of testosterone to 5α-dihydrotestosterone, than by the circulating androgen levels. In either case an analysis estimating the effect of MHID use on meningioma risk may well be confounded if not taking prostate diagnosis into account. Therefore, in our main analyses we restricted the study to men with prostatic disease to overcome this surveillance bias, and found no significant association between treatment and meningiomas. However, our study included only few cases exposed to SAA.

The third was an American retrospective interview, identifying patients through the Rapid Case Ascertainment system and state cancer register.[8] This study involved 456 meningioma patients and 452 controls who were identified by a consulting firm by random-digit dialing. This study investigated the use of LHRH and antiandrogen and risk of meningioma. There were no significant associations detected for either LHRH (OR 0.33 [95% CI: 0.07–1.66]) or antiandrogen (OR 3.82 [95% CI: 0.42–34.94]). The study was limited by low prevalence of exposed patients (exposed patients were 2 and 4, respectively), thus, the power to detect an association was not adequate. Furthermore, it was not specified if the antiandrogens were either steroidal, nonsteroidal, or both combined.

The study from the UK also examined the risk of meningioma among users of LHRH-agonists and NSAAs and found no significantly increased risks.[4] Our study supported this finding. To the best our knowledge, our study is the first to investigate the association between 5αRIs and meningiomas.

A potential limitation of our study is that patients may die with an undiagnosed meningioma, but the mean age for our cohort is relatively high when included in the study (69.9 years old). Furthermore, prostate carcinoma has a long overall survival with 10- and 15-year relative survival rates being 97.8% and 91.4%, respectively.[15] This means that most of the patients in our cohort would survive long enough to be diagnosed with a potential meningioma, thereby reducing this potential limitation. Our study was limited by the small number of users of some drug types to determine specific risks of these types.

Several strengths substantiate this study. The access to detailed and complete register information of medicine-use allowed construction of a complete cohort of male hormone-interfering drug users within the same disease groups, thereby diminishing the important limitations of surveillance bias, as seen in the previous studies. This is very important, since a large number of incidental meningioma patients are diagnosed during diagnostic work-up related to cancers (diagnostic workup for brain metastases). The fact that there, in Denmark, is free universal access to healthcare ensured that patients displaying new neurological symptoms undergoes relevant diagnostic tests. Furthermore, patients diagnosed with neurofibromatosis type II or meningioma at baseline were excluded.

In conclusion, we found no evidence of increased short- or long-term risk of meningioma in prostate patients treated with male hormone-interfering drugs.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

Keywords

cohort study | male hormone-interfering drugs | meningioma | prostate cancer | prostate hyperplasia.

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Authorship

Data management: Jørgen Vinsløv Hansen and Jan Wohlfahrt. Concept and design: All authors. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Laura Giraldi. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Jørgen Vinsløv Hansen, Jan Wohlfahrt. Obtained funding: Laura Giraldi. Supervision: Tina Nørgaard Munch, Mads Melbye, Kåre Fugleholm.

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