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The Risk of New Onset Dementia and/or Alzheimer Disease among Patients with Prostate Cancer Treated with Androgen Deprivation Therapy: A Systematic Review and Meta-Analysis

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Abbreviations and Acronyms

AD = Alzheimer disease

ADT = androgen deprivation therapy

GnRH = gonadotropin-releasing hormone

PCa = prostate cancer

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Purpose: Androgen deprivation therapy is a standard therapy for some patients with localized and almost all patients with metastatic prostate cancer. Although several clinical cohort studies have identified an impact of androgen deprivation therapy on cognitive function, the previous reviews were not able to perform a well designed quantitative synthesis to summarize the risk of dementia and/or Alzheimer disease. Consequently there is still a lack of systematic review and meta-analysis regarding the impact of this risk including more recent studies.

Materials and Methods: We conducted a systematic review and meta-analysis of the literature assessing the differential incidence of dementia and/or Alzheimer disease as outcomes in patients with prostate cancer who did vs did not receive androgen deprivation therapy. We queried PubMed® and Web of Science™ databases from January 1 to 3, 2020. We used random or fixed effects meta-analytic models in the presence or absence of heterogeneity per the I^2 statistic. We performed 6 meta-analyses for all cause dementia, Alzheimer disease and all cause dementia or Alzheimer disease according to the duration of androgen deprivation therapy (up to 12 or more than 12 months).

Results: A total of 14 studies were selected after considering inclusion and exclusion criteria. Nine of them reported all cause dementia (ie all types of dementia including Alzheimer disease), with 8 reporting Alzheimer disease. Five studies assessed these outcomes according to the duration of androgen deprivation therapy. The risk of new onset dementia (all cause) and Alzheimer disease was higher in patients with prostate cancer who received androgen deprivation therapy compared to those who did not (HR 1.21, 95% CI 1.11−1.33 and HR 1.16, 95% CI 1.09−1.24). The risk of dementia (all cause) was higher in patients with prostate cancer who received androgen deprivation therapy for more than 12 months (HR 1.36, 95% CI 1.07−1.72); however, for those who had less than 12 months of androgen deprivation therapy exposure the difference was not statistically significant 1.06 (95% CI 0.77−1.28). There was no association between the androgen deprivation therapy duration and the risk of Alzheimer disease (HR 1.21, 95% CI 0.97−1.51 for exposure up to 12 months and HR 1.39, 95% CI 0.69−2.79 for exposure greater than 12 months).

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Conclusions: Men who receive androgen deprivation therapy for prostate cancer have an increased risk of dementia and/or Alzheimer disease compared to men who do not receive androgen deprivation therapy; this was more pronounced when androgen deprivation therapy was given longer than 12 months.

Key Words: androgen antagonists, Alzheimer disease, dementia, prostatic neoplasms

It is estimated that 50% of patients with prostate cancer will eventually receive androgen deprivation therapy during the course of their disease management.[1] Androgen receptor messenger RNA was found to be expressed in cortical brain regions that are critical for cognitive functions (eg the prefrontal cortex, parietal lobe and hippocampus). Dihydrotestosterone, which functions as a transcription factor, has a higher affinity binding to androgen receptor.[2] Moreover, studies used functional magnetic resonance imaging to assess the effect of androgen deprivation therapy on cerebral structures and its potential association with cognitive function deterioration in patients with prostate cancer undergoing androgen deprivation therapy.[3] These studies showed a decrease in the gray matter volume in the frontopolar cortex, dorsolateral prefrontal cortex and primary motor cortex in patients with prostate cancer under androgen deprivation therapy.[4] An association has also been shown between low level of testosterone and the risk of Alzheimer disease.[5] Furthermore, an Alzheimer disease diagnosis has been found to be inversely associated with the free testosterone index (the ratio of serum testosterone to sex hormone binding globulin).[6] Testosterone supplements were also found to have a positive effect on cognitive functions.[3,7–9]

ADT is indicated in a broad group of patients with PCa in conjunction with radiation therapy for intermediate and high risk localized disease, locally advanced disease, disease recurrence after initial local therapy and metastatic disease.[10–12] The most common side effects of ADT are sexual dysfunction, osteoporosis with an increased risk of bone fractures, cardiovascular disease, new onset noninsulin dependent diabetes mellitus and decrease in muscle mass in conjunction with an increase in fat.[12,13]

The risk of cognitive disorders such as dementia and/or AD in patients with PCa who have received ADT has been described in several studies.[3,14] Indeed, the International Society of Geriatric Oncology recommends that clinicians discuss the risk of cognitive dysfunction with older patients with PCa who are considered for ADT.[15] This recommendation is mainly based on the systematic review and meta-analysis by Sun et al, who found a higher risk, albeit not statistically significant, of overall cognitive impairment after ADT (HR 1.28, 95% CI 0.93–1.76).[14] However, their meta-analysis suffered from some limitations such as including cohort studies with different outcome definitions as well as few studies that included quantitative synthesis. Given there are different types and pathophysiology of dementia, ADT may have a different effect on these different types (eg Alzheimer disease as the most common type, followed by vascular dementia, Lewy body dementia, mixed dementia, frontotemporal degeneration and dementias associated with brain injury, infections and alcohol abuse).[16]

Therefore, we aimed to perform a systematic review and meta-analysis of the available literature to assess the risk of dementia and/or AD (as the most common type) among patients with PCa who received ADT. We hope to strengthen the evidence so as to solidify the ADT specific recommendations by guidelines, thereby improving counseling and consequently elucidating decision making.

METHOD AND MATERIAL

In this meta-analysis we followed the MOOSE (Meta-analyses of Observational Studies in Epidemiology) statement guidelines, which propose a checklist of items for reporting that builds on similar activities for randomized controlled trials,[17] and also the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The proposed checklist by the MOOSE group contains specifications for the reporting of meta-analyses of observational studies, including background, search strategy, methods, results, discussion and conclusion. The group recommends the reporting of quality scoring and also subgroup or sensitivity analysis rather than quality scores as weights in the analysis.[17]

Eligibility Criteria

The question of this study was, "Are prostate cancer patients who receive ADT at a higher risk of dementia and/or Alzheimer disease compared to those who do not receive ADT?" All current articles covering the study question were eligible for this systematic review. ADT for PCa was defined as having received GnRH agonist or antagonist. We selected studies that performed quantitative synthesis according to the similarity in PICO elements (Patient/Problem, Intervention, Comparison and Outcome) to decrease the selection bias and heterogeneity. The inclusion criteria for the quantitative meta-analysis were original research articles that assessed dementia and/or AD as an outcome and reported an estimated risk effect (hazard ratio, odds ratio, relative risk) for both patient and control groups. Exclusion criteria included use of disease-free population as a control group, other types of ADT than GnRH agonists/antagonists as an intervention group (for example antiandrogens only or

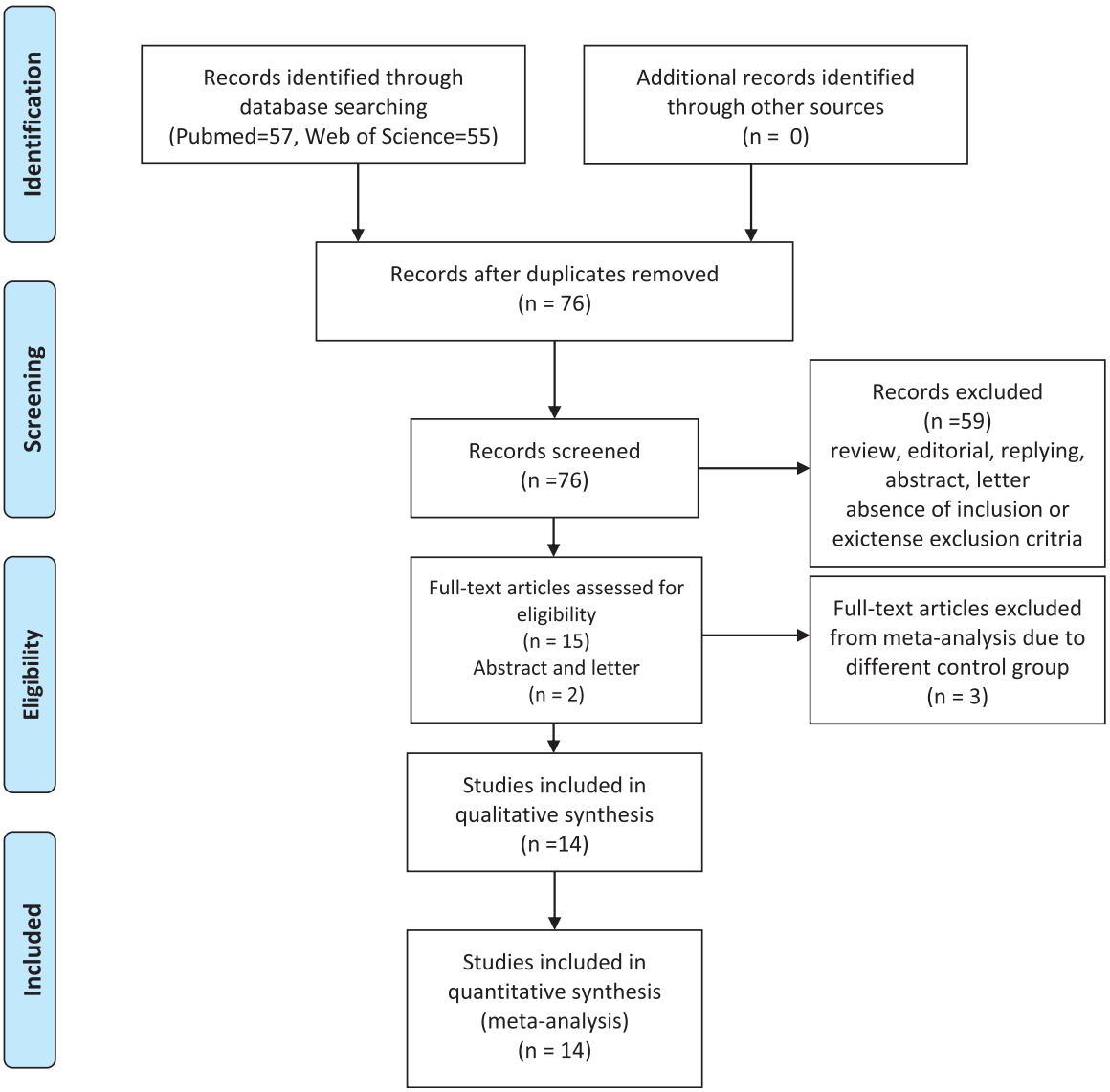

Figure 1. Selection process of articles to assess risk of dementia and/or Alzheimer disease in patients with prostate cancer on androgen deprivation therapy.

orchiectomy). Therefore, we used broad inclusion criteria and then applied exclusion criteria to control heterogeneity of design and outcomes.[17] Consequently the more comparable cohort studies according to the MOOSE guidelines were included in analyses. Furthermore, the heterogeneity of the population was explored by detecting the source and country of databases. We have categorized outcomes of studies to all cause dementia or AD and dementia, according to reported International Classification of Diseases codes in the literature.

Information Sources

We searched PubMed and Web of Science for studies published before January 1, 2020. The search queries line and search strategies were "((prostate OR prostatic) AND (cancer OR carcinoma) OR (prostatic neoplasms[MeSH®])) AND ADT OR androgen suppression OR androgen deprivation therapy [MeSH] OR androgen antagonists [MeSH]) AND (Alzheimer OR dementia [MeSH])" in PubMed and "((prostate OR prostatic) AND (cancer OR carcinoma)) AND (ADT OR androgen suppression OR androgen deprivation therapy OR chemical castration) AND (dementia OR Alzheimer)" in Web of Science.

The search results were restricted to English language articles. Title and abstract screening were done independently by 2 reviewers; any disagreement about eligibility of the articles was resolved by Delphi consensus with the coauthors. Data extraction sheet developed based on the Cochrane Consumers and the Communication Review Group's data extraction template was used (http://cccrg.cochrane.org/author-resources). We extracted the following data: first author, type of article, year of publication, dates of the data collection or enrollment, cohort type, sample size, number of individuals on ADT, outcome, how the outcome was measured, type of effect statistic, effect statistic error measures and effect statistic p value. There were no limitations in the data of the articles, so we did not need to

contact any authors for additional details. Modified Newcastle-Ottawa scale criteria were used to assess the quality of the included studies.[18] Subsequently HR and 95% CIs with dementia (all cause), dementia and AD as outcomes were retrieved, and all discrepancies regarding data extraction were resolved by Delphi consensus with coauthors.

Statistical Analysis

Forest plots were used to assess the multivariable HRs. We summarized them to depict the relationship of all cause dementia (ie, all types of dementia including Alzheimer disease) or AD with ADT. When only HRs and p value were reported, we calculated the corresponding 95% CIs. We included whether the comparison groups received less or more than 12 months of ADT for the duration effect of ADT. We utilized multivariable adjusted or propensity score matched analyses in the quantitative meta-analyses. Studies that included to perform meta-analyses used variables in adjusting of the patients and control groups. These variables were demographic, socioeconomic characteristics, physical activity, medical history (eg, diabetes, hypertension), drug history, behavioral characteristics, prostate cancer stage and treatment characteristics. Primary meta-analysis included all studies that reported all cause dementia as an outcome. Secondary meta-analysis was conducted including studies that reported AD as an outcome, and the next 4 meta-analyses were conducted among studies that reported the risk of all cause dementia or AD according to the duration of ADT. We used the cutoff of 12 months due to its widespread use among reports. Heterogeneity across the studies was appraised using p values, and Q and I^2 statistics.[19] In the presence of statistically significant heterogeneity (greater than 50%) random effect meta-analysis was used. When no significant heterogeneity was observed, the fixed effect model was used. A sensitivity analysis was performed by excluding some studies that reported very different results than other studies to explore the heterogeneity.[20] However, heterogeneity of population, design and outcomes are expected when combining observational studies.[17] Funnel plots were used to detect the risk of publication bias. However, we did not use the test for funnel plot asymmetry as its power is too low in meta-analyses with fewer than 10 studies.[21] Statistical analyses were considered significant if the p value was less than 0.05. All analyses were carried out using Stata® version 14.

RESULTS

After initial screening 76 articles were available for assessment. The selection process of the systematic review is shown in figure 1. After further assessment according to inclusion and exclusion criteria, 14 studies were available for the systematic review and meta-analysis. Therefore, we excluded the studies by Hershman,[22] Robinson[23] and Ng[24] et al from the meta-analyses because they had a different control group (ie, ADT continuous vs ADT intermittent and ADT vs disease-free population). The study by Chung et al had a different control group (disease-free population) for the primary end point but in subanalysis they used patients with PCa without ADT as a control group.[25] We only included studies that had all causes of dementia and/or AD as the outcome end point to perform the meta-analysis (supplementary table, https://www.jurology.com).

Almost all of the studies in this review excluded patients with probable bias effect such as prior chemotherapy, any history of cognitive disorders and/or cerebrovascular accidents. Of the 14 studies included 9 assessed all causes of dementia (ie all types of dementia including AD), 8 assessed AD and 2 assessed dementia (ie, all types of dementia excluding AD).[25–38] The quality assessment of the included studies is summarized in table 1. In general, there was not a poor quality study, and of 14 studies 10 had good quality, while the others had fair quality. The studies by Chung,[25] Khosrow-Khavar[31] and Kao[32] et al suffered from poor comparability, and their data sets did not contain possible covariants such as tobacco use, alcohol consumption, physical

Table 1. *Newcastle-Ottawa scale for all studies in quantitative synthesis*

References	Sample Size	Selection Score	Comparability Score	Outcome Score	Total Score	Agency for Healthcare Research and Quality Standards
Krasnova et al[26]	100,414	****	**	**	8	Good
Tully et al[27]	9,117	****	**	**	8	Good
Jayadevappa et al[35]	154,089	****	**	**	8	Good
Tae et al[28]	37,549	****	**	**	8	Good
Nguyen et al[29]	201,797	****	**	**	8	Good
Deka et al[30]	45,218	***	*	**	6	Fair
Baik et al[36]	1,238,879	****	**	**	8	Good
Khosrow-Khavar et al[31]	30,903	****	*	**	7	Good
Jhan et al[37]	24,360	****	**	**	8	Good
Kao et al[32]	1,314	***	*	**	6	Fair
Nead et al[33]	9,272	****	**	**	8	Good
Chung et al[25]	1,335,5,340	***	*	**	6	Fair
Nead et al[38]	16,888	****	**	**	8	Good
Capitanio et al[34]	7,081	***	*	**	6	Fair

According to Newcastle-Ottawa scale, stars were awarded for each quality item such that highest quality studies were awarded up to 9 stars.

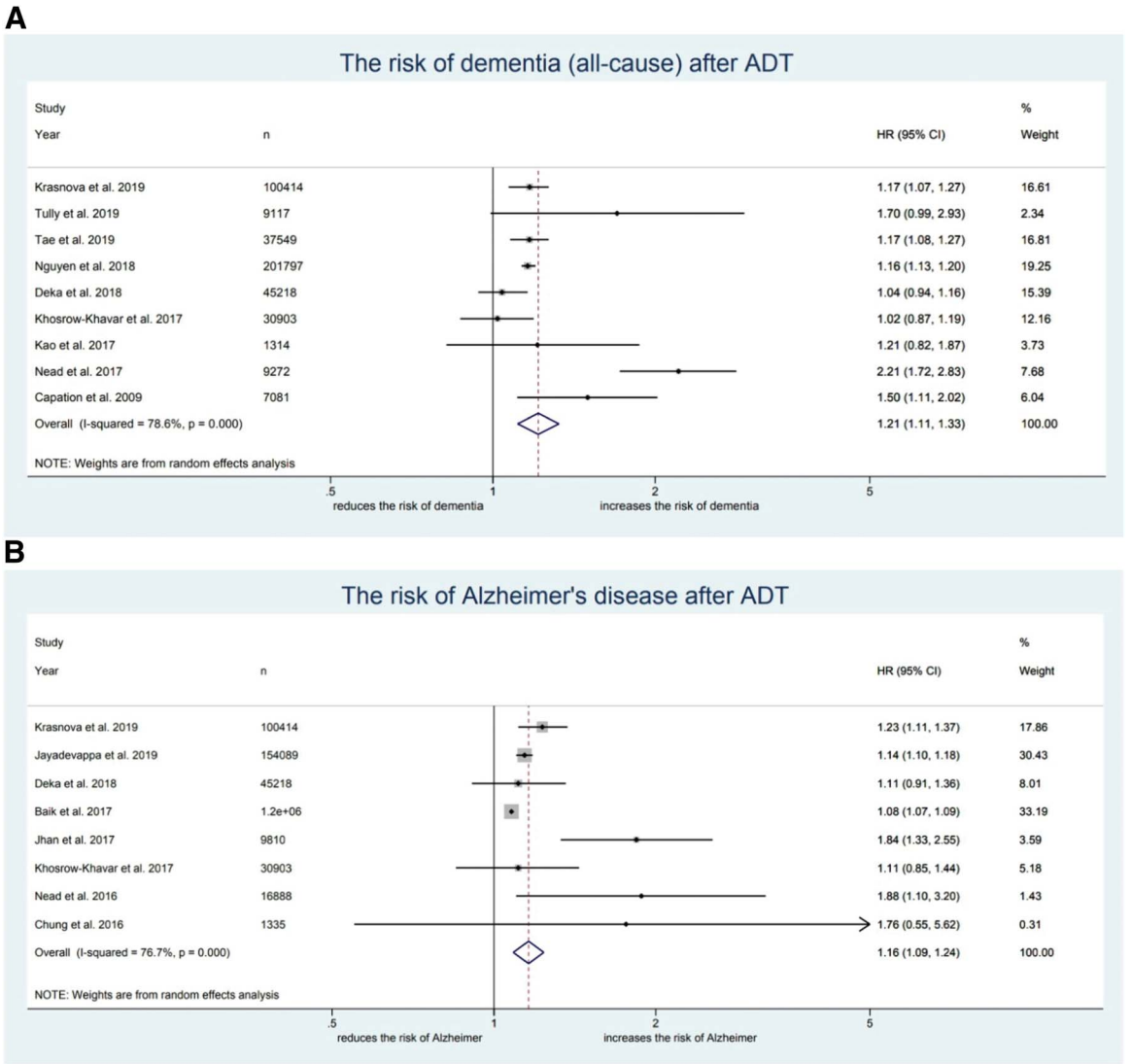

Figure 2. Forest plots with summary hazard ratios for risk of all cause dementia (*A*) and Alzheimer disease (*B*)

activity, socioeconomic status, educational level etc. Moreover, the study by Khosrow-Khavar et al had some limitations in the outcomes measurement due to event definition that was based on diagnoses recorded by general practitioners.[31] The study by Deka et al had sample selection bias, including only veterans with PCa treated with radiotherapy;[30] therefore, there were some differences in socio-demographic characteristics.

Association of All Cause Dementia and ADT Use

In the meta-analysis of all cause dementia risk 9 studies were included.[26–34] We found that ADT increased the risk of all cause dementia by a HR of 1.21 (95% CI 1.11–1.33, fig. 2). The 9 studies included in the meta-analysis evidenced high heterogeneity (I^2 78.6%, p=0.000), so a random effect model was used. The funnel plot was slightly asymmetrical (supplementary fig. 1, https://www.jurology.com). In the sensitivity analysis we excluded the study by Nead et al.[33] This was due to a very different HR (2.21, 95% CI 1.72–2.83) that was reported vs a HR lower than 1.5 in all studies that found a statistically significant increased risk of dementia after ADT.[26,28,29,34] Consequently we found that ADT increased the risk of all cause dementia by a HR of 1.15 (95% CI 1.12–1.18), and mild heterogeneity was observed (I^2 38.6%, p=0.122; supplementary fig. 2, https://www.jurology.com).

Association of Alzheimer Disease and ADT Use

In the meta-analysis of AD risk 8 studies were included.[25,26,30,31,35–38] We found that ADT increased the risk of AD by a HR of 1.16 (95% CI 1.09–1.24, fig. 2). The 8 studies included in the meta-analysis evidenced high heterogeneity (I^2 76.7%, p=0.000), so a random effect model was

Table 2. *Characteristics of studies assessing risk of dementia and Alzheimer disease based on duration of ADT*

References	Sample Size	Outcome		Duration Cutoff	Statistically Significant Increased Risk by Longer Duration	
		AD	Dementia		Yes	No
Krasnova et al[26]	100,414	✓	✓	1-6 Mos—7 mos or more	✓	
Tully et al[27]	9,117		✓	12 Mos or less—more than 12 mos	Could not assess due to sample size limitation	
Tae et al[28]	37,549		✓	12 Mos or less—more than 12 mos	✓	
Jayadevappa et al[35]	154,089	✓	✓	1—4 Doses, 5—8 doses, more than 8 doses	✓	
Nead et al[33]	9,272		✓	12 Mos or less—more than 12 mos	✓	
Deka et al[30]	45,218	✓	✓	12 Mos or less—more than 12 mos		✓
Khosrow-Khavar et al[31]	30,903		✓	6-12 Mos—12-18 mos		✓
Nead et al[38]	16,888	✓		12 Mos or less—more than 12 mos	✓	

used. The funnel plot was asymmetrical (supplementary fig. 1, https://www.jurology.com). In the sensitivity analysis we excluded the studies by Jhan[37] and Nead[38] et al, which reported HR 1.84 (95% CI 1.33−2.55) and HR 1.88 (95% CI 1.1−3.2) for the risk of AD after ADT, respectively. A HR lower than 1.23 was reported in all studies that found a statistically significant increased risk of AD after ADT.[26,35] Additionally we excluded the study by Baik et al, which reported a HR of 1.08 (95% CI 1.07−1.09) due to a very different sample size (1,238,879),[36] indeed, more than tenfold the upper limit of sample size in other studies. Consequently we found that ADT increased the risk of AD by a HR of 1.15 (95% CI 1.11−1.19), and mild heterogeneity was observed (I^2 0.0%, p=0.646).

Association of All Cause Dementia and Alzheimer Disease and ADT Duration

In our 4 later meta-analyses we assessed the combined risk of all cause dementia or AD according to the duration of ADT (less vs more than 12 months). This last analysis was limited by the different duration cutoff and small sample size (3 and 2 studies for all cause dementia and AD, respectively).[28,30,31,33,38] We found a statistically significant increased risk of all cause dementia with ADT duration of more than 12 months by a HR of 1.36 (95% CI 1.07−1.72), although not with ADT duration of less than 12 months by a HR of 1.06 (95% CI 0.77−1.28). ADT was not associated with an increased risk of AD when used for more than 12 months or up to 12 months by a HR of 1.39 (95% CI 0.69−2.79) and 1.21 (95% CI 0.97−1.51), respectively. The forest plots and funnel plots are provided in supplementary figures 1 to 4, https://www.jurology.com).

DISCUSSION

Using a systematic review and meta-analytical approach, we found that the risk of new onset dementia (ie, all cause dementia) and/or AD was increased in patients with PCa who receive ADT compared to who do not receive ADT. The risk of AD seemed to some degree lower than for dementia (HR 1.16 vs 1.21, respectively). Based on these data and the existing literature, this means that health care workers need to anticipate and manage proactively these side effects in patients with PCa prior to initiation of ADT. Three retrospective cohort studies assessed the risk of dementia and/or AD after ADT compared to a disease-free population (1 and 2 studies, respectively).[23−25] They did not find an increase in the risk of AD, but they found an increased risk of dementia. The difference between these results and the results from our meta-analysis could be related to differences in the control groups. Comparison between the disease-free population and patients with PCa who receive ADT may not be adequate as these cohorts are not comparable since they do not stem from the same source population and do not meet the same inclusion criteria.[39] For example the study by Chung et al assessed the risk of AD in patients with PCa who received ADT compared to a disease-free population and found no increased risk of AD.[25] In a subgroup analysis they compared these patients with PCa to those who did not receive ADT, and in this case found a different risk of AD.

Study design and variables that were used to perform adjusted analysis are the most crucial difference between studies that are included in this meta-analysis. Krasnova,[26] Nguyen,[29] Jayadevappa[35] and Baik[36] et al reported similar outcomes to our meta-analysis results. All of them used important variables to perform adjusted analysis (eg, socioeconomic, educational characteristics and physical activity). Those variables are important modifiable dementia risk factors in the general population.[16] Two small cohort studies[25,32] and Khosrow-Khavar et al[31] reported conflicting results with our meta-analysis results, while they did not use such variables for adjusting of study groups due to limitations of their data bases. Additionally 4 large cohort studies with a sample size of more than 1,000 included in the primary and secondary meta-analysis all found an association between ADT and increased risk of dementia and/or AD.[26,29,35,36]

Large sample size is an essential factor in a retrospective cohort study, especially when studying a rare outcome.[40] Studies that did not find an association between ADT and dementia and/or AD have usually suffered from small sample size and/or had lower sample size.[25,30–32]

We also examined whether ADT duration could have an association with new onset dementia and/or AD. In our meta-analysis we found that patients who receive ADT for a duration of 12 months or more have a statistically significantly increased risk of new onset dementia compared to patients who receive a shorter duration. The risk of developing AD, however, was not found to be associated with longer ADT duration. This lack of association in our study can either be due to the small sample size or it could be a true absence of an association, with the first being more probable. Several other studies have evaluated the duration of ADT as a risk factor for dementia and/or AD and, despite the discrepancies in the definitions of the duration cutoff time within published studies, the results consistently show a higher risk in patients who received ADT for a longer duration (table 2).[24,26–28,30,31,33,35,38] One randomized controlled study assessed the duration of ADT and the risk of dementia in patients who received continuous vs intermittent ADT.[22] Dementia was observed in 8% of patients receiving continuous ADT and 4% of those receiving intermittent ADT (HR 1.98, $p=0.07$). The results were not comparable to our findings; however, these results should be interpreted with caution given the low number of reported events.

Our review has limitations that should be acknowledged. The main limitation is the retrospective nature of the studies included. Another limitation is the differences between study designs with different intervention groups (GnRH agonist or antagonist, orchiectomy and antiandrogens or different ADT duration), control groups (patients with PCa or disease-free population) and outcomes (all cause dementia, dementia or AD). However, we have only performed the analysis for studies that have comparable groups. Dementia and/or AD have a multifactorial pathophysiology with modifiable and nonmodifiable (eg age) risk factors in the general population.[16] Those risk factors as well as ADT type[23,31,37] and duration of ADT all should be considered in studies to determine the risk of new onset dementia and/or AD in patients with PCa under ADT (supplementary fig. 5, https://www.jurology.com). Lack of attention to all of those variables is the main gap between current studies that assess the impact of ADT on increased risk of dementia and/or AD.

CONCLUSIONS

Patients with PCa who receive ADT have an increased risk of new onset dementia and/or AD compared to those who do not receive ADT. This risk can further increase with ADT duration of more than 12 months. Based on these findings, we recommend routine monitoring of cognitive function in patients receiving ADT. In addition, mental/cognitive status assessment should be performed in all patients planned for ADT. Adequate patient counseling about these potential side effects of ADT should be part of the decision making and followup strategy. However, prospective studies need to strengthen evidence that supports these recommendations. Thus, all variables that have a potential influence on outcomes should be considered to perform adjusted analysis in future studies (ie, the risk factors of dementia in the general population as well as ADT type and duration of ADT). Moreover, there are different types and different pathophysiologies of dementia, and the ADT effect on these different types of dementia should be assessed.

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