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Original article

Association of androgen deprivation therapy and depression in the treatment of prostate cancer: A systematic review and meta-analysis

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Abstract

Background: There is increasing evidence that androgen deprivation therapy (ADT) may be associated with depression. Existing studies have shown conflicting results.

Methods: PubMed, Web of Science, Embase, and PsycINFO were queried on April 5, 2017. Eligible studies were in English and reported depression among individuals with prostate cancer exposed to a course of ADT vs. a lesser-exposed group (e.g., any-ADT vs. no ADT and continuous ADT vs. intermittent ADT). We used the MOOSE statement guidelines and the Cochrane Review Group's data extraction template. Study quality was evaluated by Newcastle-Ottawa Scale criteria. We conducted a random-effects meta-analysis to calculate summary statistic risk ratios (RRs) and 95% CIs. Heterogeneity was quantified using the I^2 statistic and prespecified subgroup analysis. Small study effects were evaluated using Begg and Egger statistics.

Results: A total of 1,128 studies were initially identified and evaluated. A meta-analysis of 18 studies among 168,756 individuals found that ADT use conferred a 41% increased risk of depression (RR = 1.41; 95% CI: 1.18–1.70; $P < 0.001$). We found a consistent strong statistically significant association when limiting our analysis to studies in localized disease (RR = 1.85; 95% CI: 1.20–2.85; $P = 0.005$) and those using a clinical diagnosis of depression (RR = 1.19; 95% CI: 1.08–1.32; $P = 0.001$). We did not find an association for continuous ADT with depression risk compared to intermittent ADT (RR = 1.00; 95% CI: 0.50–1.99; $P = 0.992$). There was no statistically significant evidence of small study effects. Statistically significant heterogeneity in the full analysis ($I^2 = 80\%$; 95% CI: 69–87; $P < 0.001$) resolved when examining studies using a clinical diagnosis of depression ($I^2 = 16\%$; 95% CI: 0–60; $P = 0.310$).

Conclusion: The currently available evidence suggests that ADT in the treatment of prostate cancer is associated with an increased risk of depression.

Keywords: Androgen deprivation therapy; Depression; Prostate cancer; Behavioral symptoms; Hormone therapy

1. Introduction

Androgen deprivation therapy (ADT) has a demonstrated survival benefit for metastatic and locoregional prostate cancer [1]. An estimated 50% of men with prostate cancer ultimately use ADT [2], and this proportion may continue to grow with recent randomized evidence supporting a survival benefit in the salvage setting [3]. With over a million new diagnoses of prostate cancer each year [4], the implications of adverse effects of ADT are substantial.

In contrast to the demonstrated survival benefit, ADT has been associated with numerous adverse effects including cardiometabolic and neurocognitive dysfunction [5,6]. A recent large population-based study demonstrated a positive association between ADT and depression risk [7]. However, although some studies support this association [8–11], other studies do not [12–16]. Currently, the true association between ADT and depression is unclear. In this study, we undertake a systematic review and meta-analysis to examine the association of ADT in the treatment of prostate cancer and depression risk.

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2. Methods

The MOOSE statement guidelines were used for this systematic review and meta-analysis [17].

2.1. Eligibility criteria

We included full-text articles in English that reported the outcome of depression (e.g., billing codes and depression inventory) among individuals with prostate cancer exposed to ADT vs. a lesser-exposed comparison group (e.g., any-ADT vs. no ADT and continuous ADT vs. intermittent ADT). Inclusion criteria for the quantitative meta-analysis were studies that reported an effect estimate (e.g., risk ratio [RR]) and measure of error (e.g., CI) or reported measurement of or adjustment for depression that could be used to calculate an effect estimate and measure of error.

2.2. Information sources

We carried out electronic searches in PubMed (1966-present), Web of Science (1945-present), Embase (1966-present), and PsycINFO (1806-present). The search was undertaken on April 5, 2017. Each database was searched for prostate cancer and ADT and depression terms. Detailed search strings for each database can be found in Supplementary Fig. 1. We additionally queried the reference lists of included articles. Two investigators (S.S. and D.Y.) independently assessed the eligibility of each study by using the title and abstract for initial screening followed by review of the full text and data extraction with consensus reached by discussion with a third investigator (K.N.) as needed. We used a data extraction sheet developed based on the Cochrane Consumers and Communication Review Group's data extraction template (http://cccrg.cochrane.org/author-resources). Searchers extracted the following items from each study: first author, type of article, study location, year of publication, dates of data collection or enrolment, study design (e.g., prospective or retrospective), local vs. metastatic disease, sample size, number of individuals on ADT, details of ADT use, how the outcome was delineated (e.g., International Classification of Diseases-9 codes and depression inventories), number of events in each group, type of effect statistic, measure of error, methodology to account for confounding, length of follow-up, whether comparison groups were derived from the same population, and whether prevalent depression was accounted for in the analysis. We assessed the internal validity of each study included in the qualitative review based on modified Newcastle-Ottawa Scale criteria [18]. We attempted to contact corresponding authors of all articles at least twice to provide missing descriptive details and summary data for inclusion in the quantitative meta-analysis.

2.3. Statistical analysis

We conducted a meta-analysis to calculate summary statistic RRs and 95% CIs for the risk of depression in patients with prostate cancer exposed to a course of ADT vs. a lesser-exposed comparison group (e.g., any-ADT vs. no ADT and continuous ADT vs. intermittent ADT). We included comparison groups exposed to a lesser amount of ADT given evidence for a dose effect of ADT on depression risk [7]. In our primary meta-analysis, we included all eligible studies reporting a binary depression outcome. Where eligible studies or subgroups were clearly overlapping, we included the study or subgroup with the largest number of events, or the largest sample size if the number of events was not available in subgroup. Additionally, if depression was evaluated at multiple time points, the effect estimate from the longest on ADT time point was used. Ratios of rates, odds ratios, and RRs were considered equivalent measures of risk [19,20]. Studies with zero events in a comparison arm were included per the Cochrane Handbook guidelines [22].

The proportion of heterogeneity due to study variation was quantified using the I^2 statistic [21]. Random-effects meta-analytic models were selected *a priori* as a more conservative approach given expected variability in methods used to determine depression status and diversity of study populations. Heterogeneity was explored per the Cochrane Handbook for Systematic Reviews of Interventions [22]. We present summary data for prespecified subgroups including by study design (prospective, retrospective, and cross-sectional), whether confounding was accounted for in the analysis, by method used to determine depression (e.g., clinical diagnosis such as International Classification of Diseases-9 code vs. depression inventory), and whether studies were limited to localized disease. We did not undertake statistical comparisons within or across subgroups given the limitations of this approach in meta-analyses [22].

The presence of small study effects was evaluated by visualization of a funnel plot and calculating Begg and Egger statistics. Tests were considered significant if the two-sided P value was less than 0.05. All analyses were carried out using Stata version 12 (StataCorp, College Station, TX).

3. Results

Our study selection process is summarized in Fig. 1. In total, we reviewed 795 studies by title and abstract after duplicate removal with 52 studies undergoing full-text review. We excluded 26 studies after full-text review because they did not examine individuals with prostate cancer exposed to ADT vs. a lesser-exposed group ($n = 22$) or did not examine depression as an outcome ($n = 4$). Twenty-six studies meeting our review inclusion criteria