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Cognitive Impairment Following Hormone Therapy: Current Opinion of Research in Breast and Prostate Cancer Patients

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Abstract

Purpose of review—Hormone therapy is a common cancer treatment that may be associated with numerous side and late effects, and in recent years, has been linked to changes in cognition. Here, we present the most important recent findings from empirical studies and reviews that have focused on the effects of hormone therapy on cognitive functioning in breast and prostate cancer populations, underline some general shortcomings, and propose directions for future research.

Recent Findings—Recent research indicates that cognitive impairment may occur in breast and prostate cancer patients following onset of hormone therapy. However, due to methodological shortcomings and heterogeneity of current research, conclusions regarding the effects of hormone therapy on cognitive functions remain tentative.

Summary—This review highlights the general findings whilst also describing the many methodological shortcomings that need to be addressed in future research. It is clear that larger scale neuropsychological studies that also evaluate the impact of impairments on daily life functioning will improve our understanding of the effects of hormone therapy on cognition and inform the development of appropriate interventions.

Keywords

androgen deprivation therapy; cancer; cognitive impairment; endocrine therapy; hormone therapy

INTRODUCTION

Breast and prostate cancer share similarities as hormone-sensitive cancers. In these cancers, the steroid hormones – androgens and estrogens – play a critical role in driving cancer growth. They act through hormone receptors stimulating cell proliferation and tumor growth [1, 2]. Given the hormone sensitivity of these cancers, antihormone therapy, simply referred

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CONFLICTS OF INTEREST

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to as hormone therapy, has become a mainstay treatment in both breast and prostate cancer. Hormone therapies work by either blocking sex hormone production or by suppressing hormone receptors in order to reduce or inhibit cell proliferation and tumor growth [3, 4]. While the clinical benefits and gains in survival time from hormone therapies are unquestionable, these treatments are often prescribed for many years and are associated with side and late effects such as mood disturbances, fatigue, and hot flashes [5, 6]. Furthermore, there is growing concern among cancer patients about cognitive impairment following the initiation of hormone therapy [7]. Given that steroid hormones play an important mediating role for healthy brain and cognitive functioning [8], these concerns may be justified.

Estrogen receptors and androgen receptors are both widely distributed in the brain, including regions like the hippocampus and cerebral cortex that are important for many cognitive functions [9, 10]. Steroid hormones may work directly at receptor sites, or through second messenger systems. For example, testosterone can act on the brain directly or via conversion to the androgen 5α-dihydrotestosterone, mediated by the enzyme 5α-reductase [11]. In both sexes, testosterone is also converted to estradiol locally in the brain by the enzyme aromatase, which is widely expressed in astrocytes and neuron populations of different brain regions [12]. Estradiol is known to have modulatory effects on the brain and cognition over the life span [8]. Importantly, estradiol has been shown to exert neuroprotective effects in both sexes [13]. Animal research has indicated that estradiol can regulate synaptic plasticity, adult neurogenesis, and cognition [13]. Evidence also suggests that estradiol can protect the brain from neurodegenerative diseases, affective disorders, and age-related cognitive decline [13]. Thus, in both men and women, estradiol may play an important role in normal brain function. The relationship between hormone therapy and cognition is further strengthened by studies on aging men and women that indicate a link between changes in testosterone and estrogen levels, and cognitive decline [8, 14–17]. Overall, hormone disruption because of hormone therapy may have detrimental effects on cognition.

Most research within the field of cancer-related cognitive impairment has focused on the effects of chemotherapy. However, in recent years, an increasing number of empirical studies and reviews have focused on the effects of hormone therapy on cognitive functioning in breast and prostate cancer populations. Here, we present the most important recent findings from these reports, underline some general shortcomings, and propose directions for future research.

METHODS

To provide an update of the literature since 2010, we undertook a systematic search in PubMed using the following search strategies and reviewed reference lists of relevant articles:

Prostate: prostate AND (cancer OR neoplasm OR oncol*) AND (‘cognitive impairment’ OR cognition OR neuropsychol*) AND (hormone OR endocrine OR ‘androgen deprivation’ OR antiandrogen OR ‘androgen suppression’)

Breast: breast AND (cancer OR neoplasm OR oncol*) AND (‘cognitive impairment’ OR cognition OR neuropsychol*) AND (hormone OR endocrine OR estrogen OR estradiol OR ‘aromatase inhibitors’ OR tamoxifen OR estradiol).

Searches were undertaken on August 9, 2016 and included review articles and original articles reporting: original empirical data, the association between hormone therapy in cancer patients and cognitive functioning as measured by neuropsychological test performance, and studies published in English in peer-reviewed journals. Abstracts were reviewed by both authors. Relevant full-texts were reviewed and selected based on the aforementioned criteria. All systematic reviews were assessed for quality using a measurement tool to assess systematic reviews (AMSTAR) [18]. An AMSTAR score from 0–4 indicates low quality; a score from 5–8 indicates moderate quality, and a score from 9–12 indicates a high quality review.

EFFECTS OF HT IN WOMEN WITH BREAST CANCER

Systematic investigations of the cognitive effects of hormone therapy in women with breast cancer began in 2000 with a large study reporting subtle adverse effects in women taking tamoxifen, a selective estrogen receptor modulator (SERM) [19] compared with a nonhormone therapy breast cancer group. SERMs and aromatase inhibitors such as anastrozole, exemestane, and letrozole, are the most commonly administered hormone therapy regimens in breast cancer patients. Overall, studies have investigated i) whether hormone therapy, irrespective of type, is associated with cognitive impairment, and/or ii) have compared the effects of different hormone therapies on cognition.

Recent Reviews

Since 2010, eight reviews have been published addressing the association of hormone therapy with cognitive impairment in breast cancer patients [20■■, 21■■, 22–26, 27■], demonstrating high interest in this topic. In this section, emphasis will be placed on the two systematic reviews and a recent narrative review [21■■].

A systematic review by Bakoyiannis et al. [27] includes 12 studies published before July 2015. Studies contrasting hormone therapy with no hormone therapy patients or healthy controls were mixed with studies contrasting different hormone therapy regimens (SERMs vs. aromatase inhibitors). One large (n=1498) study was erroneously included that comprised women at increased risk of breast cancer [28]. Aside from the inclusion of that study, the AMSTAR quality rating is 7 (moderate quality). Time since treatment onset ranged from 3–24 months and the authors focused on cognitive domains related to verbal memory, verbal fluency, attention and working memory, and motor- and psychomotor speed, but surprisingly not executive functions, which have been found to be particularly vulnerable to adverse effects associated with cancer treatments [29]. The authors concluded that there is evidence to indicate changes in cognitive functions following hormone therapy, with verbal memory being the most widely reported domain affected. However, as increases and decreases in verbal memory were reported, no clear conclusions could be made. Impairments in attention and working memory were noted, but in only two studies. The authors concluded that there was a trend favoring aromatase inhibitors over SERMs. Overall,

their conclusions need to be interpreted with caution because of the erroneous inclusion of a non-cancer study.

In a second systematic review by Lee et al. [20■■], 21 studies were included with both short (≤2 years) and long-term (>2 years) assessments after hormone therapy onset, many of which were reported in the aforementioned review [27■]. The AMSTAR quality rating is 7 (moderate quality). Studies were subdivided into three types: those contrasting hormone therapy with nonhormone therapy controls (healthy or cancer controls); those comparing different hormone therapy regimens (SERMs vs. aromatase inhibitors); and those comparing hormone therapy with chemotherapy. The authors concluded that there is evidence to suggest short and long-term cognitive impairment related to hormone therapy use with 80% of the reviewed studies finding an association. A broad range of cognitive domains were affected, including learning and memory, processing speed, language, and executive functions. No consistent patterns of difference were found between different hormone therapy regimens, or between hormone therapy use and chemotherapy, suggesting that adverse effects may occur in some individuals regardless of the type of cancer treatment.

Finally, an important narrative review was published by Zwart et al. [21■■] that included a thorough discussion of mechanisms underlying cognitive impairment associated with hormone therapy in breast cancer through an examination of clinical data and neurobiological effects observed in preclinical models. A comprehensive summary of important randomized controlled trials (RCTs) and observational studies was also presented. Results of the RCTs indicated that SERM (tamoxifen) use is associated with adverse cognitive effects, but findings were inconclusive regarding aromatase inhibitor use. The effects of hormone therapy as a whole on cognition were deemed less clear.

Despite evidence pointing to the detrimental effects of hormone therapies on cognition, the above reviews emphasized that because of small sample sizes and heterogeneity of study designs, definite conclusions could not be made. To the best of our knowledge, no published meta-analyses investigating the cumulative evidence in breast cancer patients exist, possibly because of this heterogeneity.

Recent Empirical Studies

Since the most recent systematic review, two notable studies have been published [30■, 31■]. Bender et al. [30■] investigated the effects of aromatase inhibitors on cognition, while Le Rhun et al. [31] conducted a randomized trial comparing the effects of different hormone therapies on cognition in chemotherapy-naïve breast cancer patients. Since chemotherapy may be associated with cognitive impairment on its own, studying the possible cognitive effects of hormone therapy in chemo-naïve patients is of particular importance.

The study by Bender et al. [30■] is among the largest to date that investigated the effects of aromatase inhibitors on cognition – an understudied area. Participants included postmenopausal breast cancer patients (114 received chemotherapy and aromatase inhibitors; 173 received aromatase inhibitors only) and 110 healthy education-matched controls. Neuropsychological tests were administered at baseline prior to chemotherapy and

aromatase inhibitors, and at 6, 12, and, 18 months after aromatase inhibitor onset. Eight factors were derived from 13 cognitive variables. Patients exhibited poorer executive functioning than healthy controls both before systemic treatments and throughout the study period. Although no consistent patterns of change were observed for verbal or visual memory, mental flexibility, psychomotor efficiency or attention, there was decline in visual working memory and concentration related to aromatase inhibitor use during the first six months, followed unexpectedly by improvements in these domains from 6 to 12 months, with another decline from 12 to 18 months. Effect sizes were small to medium. It should be noted that the visual working memory factor included tasks usually described as measuring visuospatial, visual memory, and executive functioning abilities.

In the trial by Le Rhun et al. [31■], 74 chemo-naïve breast cancer patients were randomized to a SERM (Tamoxifen) or aromatase inhibitors (Anastrozole, Letrozole, and Exemestane). Neuropsychological tests were administered at baseline prior to hormone therapy, and at 6 and 12 months assessing psychomotor speed, working memory, verbal and visual memory, and executive functions. The primary outcome was a test of verbal memory. There were no statistically significant differences between groups in any domain. The authors concluded that aromatase inhibitors do not have worse effects on cognition than the use of SERM. Although consistent with the conclusions of Lee et al. [20■■], the results differ from the findings of other RCTs comparing aromatase inhibitors with SERMs. For example, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) study [32] in which postmenopausal chemo-naïve women were randomized to either a SERM (n=80) or an aromatase inhibitor (n=99), showed that women receiving SERM had significantly lower processing speed scores than the aromatase inhibitor group at 12-months follow-up. Furthermore, they performed significantly worse on verbal memory and executive functioning tests than healthy controls (n=120), which was not the case in the aromatase inhibitor group. Other RCTs report worse cognitive outcomes associated with SERM, including the Breast International Group (BIG) 1–98 trial [33]. However, results from that 5-year trial may be confounded since some participants received both types of hormone therapy, and more women in the aromatase inhibitor group received chemotherapy. The same group also published data regarding hormone therapy cessation reporting moderate improvement (Cohen’s d = 0.53) in overall cognitive performance one year after hormone therapy cessation, suggesting that the detrimental effects may be reversible [34].

EFFECTS OF ANDROGEN DEPRIVATION THERAPY IN MEN WITH PROSTATE CANCER

Systematic investigations of the cognitive effects of hormone therapy (hereafter referred to as androgen deprivation therapy [ADT]) in male patients with prostate cancer began in 2002 [35]. The primary focus of these studies has been to evaluate the effect of pharmacological ADT on cognition. ADT may include the administration of luteinizing-hormone releasing hormone agonists (also known as gonadotropin-releasing hormone agonists), luteinizing-hormone releasing hormone antagonists, and oral antiandrogen such as flutamide or bicalutamide [36].

Recent Reviews

Since 2010, there have been three comprehensive reviews of the literature. An additional review prior to 2010 is also discussed, because of frequent references to it in the literature. This systematic review of 9 studies by Nelson et al. [37] receives an AMSTAR rating of 3 (low quality). It reported variable evidence for cognitive impairment following ADT, but concluded that 47–69% of ADT patients showed decline in at least one cognitive domain (over time periods ranging from 3 to 9 months). Visuospatial and executive functions were most commonly affected. The second review by Alibhai and Mohamedali [38] has an AMSTAR rating of 2 (low quality). It was essentially a critical reexamination of the studies presented by Nelson et al. [37], highlighting the inconclusive nature of results and emphasizing significant methodological shortcomings. For example, in spite of the numerous tests administered, few statistically significant differences between ADT patients and controls were generally found, and any differences were often not corroborated and sometimes even contradicted in other studies. They also highlighted problems with multiple statistical comparisons and practice effects. By 2012, another review was undertaken by Jamadar et al. [39] that included 11 studies, and has an AMSTAR rating of 4 (low quality). Similar methodological problems were noted, as well as a focus on mostly well educated samples. More robust findings were reported related to negative effects on spatial memory [40].

To address the inconsistent results in the field, small sample sizes, and lack of standardization of the cognitive domains to which tests were assigned, McGinty and colleagues [41■■] undertook a systematic review and meta-analysis of the literature to June 2012 that receives an AMSTAR rating of 9 (high quality) [42]. Fourteen studies that utilized longitudinal comparisons and/or comparisons with a prostate cancer control group or a non-cancer control group (total n = 193) were included. Cognitive domains evaluated were: attention/working memory, executive function, language, verbal memory, visual memory, visuomotor ability and visuospatial ability. Results indicated that ADT patients performed significantly worse on visuomotor tasks (involving both cognitive and manual manipulation of visual stimulus material) compared to controls (effect size, g=−0.67). There were no significant differences found in any other cognitive domain.

Recent Empirical Studies

Since McGinty et al.'s meta-analysis [41■■], there have been a few published studies of note. One important addition is the controlled study by Gonzalez et al. [43■■] that compared ADT patients (n = 58) with a matched non-ADT prostate cancer control group (n = 84) and a healthy control group (n=88). Neuropsychological assessments were conducted at baseline (before or within 21 days of starting ADT), 6 months and 12 months later. Mean level cognitive performance over time did not differ between groups. However, the ADT group was approximately two times more likely to exhibit impaired cognitive performance than the combined control group at 6 and 12 months, and they exhibited more impairment on on at least two tests tests within 12 months than the other two groups. This study improved upon earlier controlled studies by including an examination of potential moderators such as age, cognitive reserve, symptomatology (fatigue, depression and hot flashes), and genetic variants, though the study was likely underpowered to detect effects. Though not unique to

this study, their approach of comparing patients on the basis of cognitive impairment status and the number of impaired tests helped to mitigate the statistical problem of multiple comparisons. When individual test differences were examined, there was only a marginal difference on one measure of executive functioning.

Another recent study assessed cognitive abilities less frequently researched in this population. Yang et al. [44■] examined cross-sectional differences in cognitive functioning between an ADT (n=43), a non-ADT (n=35), and a healthy control group (n=40) in a Chinese population. They included tests of event-based and time-based prospective memory. The ADT group performed worse on the event-based prospective memory test than the other two groups, highlighting the potential importance of adding prospective memory tests to the standard batteries.

DISCUSSION

The aim of this review is to provide an update on recent research focused on the association between hormone therapy and cognitive function as assessed by neuropsychological tests in breast and prostate cancer patients. It is clear that cognitive impairment may occur in breast and prostate cancer patients following onset of hormone therapy, but the impaired cognitive domains associated with hormone therapy are varied. Deficits in language abilities, learning and memory, executive functioning, and processing speed may be present in breast cancer patients; and deficits in visuomotor abilities, visuospatial abilities, spatial memory, executive functioning, and possibly verbal memory may be present in prostate cancer patients, though prostate cancer patients may have a greater likelihood of impairments on visuomotor tasks [41■■]. However, findings need to be interpreted with caution because of numerous methodological shortcomings.

Studies have typically included small sample sizes and been heterogeneous in nature, with different applied research methodologies, designs, and cancer stages. For example, in the breast cancer literature, studies have focused on either the general effect of hormone therapy on cognition, or the specific effects of different hormone therapy regimens. Furthermore, differences exist regarding the included control/comparison groups (e.g., healthy controls, chemo-naïve cancer controls, and/or cancer patients who have undergone chemotherapy) making it difficult to compare studies. Even within disease groups, some studies have mixed early and advanced cancer patients who may or may not have received different treatment regimens (hormone or other). These issues make it difficult to elucidate whether the primary cause of cognitive impairment is hormone therapy, other cancer treatments, or the disease itself. This may explain why, to the best of our knowledge, there are no published meta-analyses investigating the cumulative evidence of the effect of hormone therapy on cognitive functions in breast cancer patients.

Another important and ongoing issue relates to the use of neuropsychological tests. Often, the neuropsychological test batteries used, the cognitive domains to which tests are characterized, and even the scores analyzed (i.e., raw scores, standardized z scores, composite domain scores, or global composite scores) vary across studies. For example, McGinty et al.’s visuomotor domain includes tasks often described as capturing visuospatial

abilities [41■■]. Moreover, tests often capture multiple domains at once complicating the picture even more. Furthermore, other domains not typically assessed in traditional test batteries may prove to be important to include in future research, such as prospective memory, which one study found to be impaired in ADT patients [44■■]. Thus, efforts to harmonize the tests used [29] and to categorize tests according to the cognitive domains characterized by standard reference texts (e.g., [45]) are essential. Although the use of different well selected neuropsychological tests is important for a comprehensive cognitive assessment, it continues to pose a challenge in statistical analyses, as adjustments for multiple comparisons are often not made, making findings less likely to be replicable.

An additional challenge for health care providers and patients is translating research findings into clinically meaningful outcomes. A majority of studies have focused on statistical differences between treatment groups (e.g. hormone therapy vs nonhormone therapy), but less emphasis has been placed on characterizing the clinical meaningfulness of these differences. Although guidelines have been published by the International Cognition and Cancer Taskforce (ICCTF) to operationalize and standardize clinically meaningful cognitive impairment [45], they have rarely been used (e.g., [43■■]). In group mean level comparisons, low scoring patients are often masked by high-scoring ones. The guidelines recommend a two-part criterion that facilitates a clinically meaningful measurement of cognitive impairment. Furthermore, this approach may prove useful in identifying risk factors that moderate the likelihood of hormone therapy-related cognitive changes.

Future research should explore potentially important moderators, such as age, cognitive reserve, fatigue, depressive symptoms, genetic factors, pretreatment hormone levels, menopausal status, and history of hormone replacement therapy, as they have been found to be associated with cognitive impairment in cancer or other populations [21■■, 46–50]. Indeed, in men with prostate cancer, Gonzalez et al. [43■■] examined a number of these factors and found that a genetic variant on the G protein subunit beta 3 region was associated with cognitive decline in those on ADT. There has also been promising research examining genetic variants in breast and other cancer patients, showing that individuals carrying specific genetic polymorphisms of the Apoliprotein (APOE) and catechol-O-methyltransferase (COMT) genes may be at greater risk of cognitive impairment [51–53]. An additional well known issue is that cognitive impairment may exist prior to the onset of systemic treatments such as hormone therapy and chemotherapy [54, 55] posing methodological challenges as hormone therapy-related effects may be confounded by other treatment and disease-related effects. One way to overcome these issues is to ensure the inclusion of a well matched noncancer control group, as well as a cancer control group.

The main focus of research in this area has been on impairments to cognition as measured by neuropsychological tests, but not on their impact on daily life functioning. Patient and caregiver studies using quantitative and qualitative approaches to examine self-reported or observed cognitive impairments and their impact upon daily life functioning are also necessary. Indeed, such work has highlighted areas of concern not typically measured by neuropsychological tests, such as prospective memory and multi-tasking in ADT patients [56] and the real-life impact of hormone therapy on activities of daily living, work functioning, and relationships [57–59]. It is also possible that self-report of cognitive

complaints may be more sensitive to subtle cognitive changes than neuropsychological tests [60]. Population-based studies may also provide important data about the clinical impact of hormone therapy. For example, Kao et al. investigated ADT use and dementia risk in prostate cancer patients in Taiwan and found no difference in dementia risk between ADT and non-ADT populations [61].

Our discussion highlights the importance of the many studies that have pushed the field forward and contributed to our growing understanding of the impact of hormone therapies on cognitive functioning. However, more large-scale studies are still needed to increase our knowledge regarding the nature and severity of hormone therapy-related cognitive impairments. Collaborative efforts across institutions are likely necessary to improve the standardization of methodologies, thus creating the potential for pooling of data and/or higher quality meta-analyses. Future research will also benefit from longer follow-up periods to determine the effects of hormone therapy beyond 1 or 2 years after onset of treatment and after cessation of treatment. In breast cancer, for example, hormone therapy cessation has been associated with a moderate improvement in overall cognitive performance 1 year later [34]. As evidence accumulates regarding hormone therapy-related cognitive impairment, there will be a greater need to better understand underlying neurobiological and pathophysiological mechanisms. So far, only a few studies have explored biomarkers and other potential correlates of cognitive functioning in hormone therapy patients. For example, investigators have examined neuronal activation in ADT patients and have found altered activation patterns [62, 63] and changes in brain structure [64]. However, until there is more definitive evidence regarding the association between hormone therapy use and cognitive impairment, investigations into neurobiological and pathophysiological mechanisms should, in our opinion, be secondary or an adjunct to well controlled neuropsychological studies.

Owing to growing concern among cancer patients about cognitive impairment [65, 56], it is important to comment on potentially efficacious interventions to ameliorate hormone therapy-induced cognitive impairment, even if somewhat premature. A recent review of the clinical and basic studies suggested that exercise may be beneficial for treating hormone therapy-induced cognitive impairments in women treated for breast cancer [66]. Furthermore, interventions found to be helpful for the treatment of cognitive impairment in cancer and other populations may be appropriate [67].

CONCLUSION

In summary, the research suggests that a subgroup of breast and prostate cancer patients undergoing hormone therapy may experience cognitive impairment, but future research is needed, including larger scale neuropsychological studies that also evaluate impact on daily life functioning. Such studies would greatly enhance our understanding of the nature, severity and impact of hormone therapies on cognitive functioning in cancer patients.

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KEY POINTS

- A subgroup of breast and prostate cancer patients on hormone therapy may experience cognitive impairment.
- The cognitive domains affected in both disease groups are varied, but a recent meta-analysis indicates that prostate cancer patients on ADT may experience more problems in visuomotor functioning.
- Numerous methodological shortcomings limit our ability to make definitive conclusions about the effects of hormone therapy on cognition in cancer patients.
- Large scale well controlled neuropsychological studies that also evaluate the impact of cognitive impairment on daily life functioning is of greater priority than an examination of mechanisms, as we still do not have a consistent, clear understanding of the nature, severity and impact of hormone therapy on cognition in cancer patients.
- Population-based studies that evaluate relative risks of cognitive disorders associated with hormone therapies would also enhance our understanding of the impact of hormone therapies on cancer patients.