Course and Moderators of Hot Flash Interference during Androgen Deprivation Therapy for Prostate Cancer: A Matched Comparison

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Abbreviations and Acronyms

ADT = androgen deprivation therapy

BMI = body mass index

HFI = hot flash interference

SNP = single nucleotide polymorphism

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Purpose: Many men receiving androgen deprivation therapy for prostate cancer experience hot flashes. This study aimed to describe the course of hot flash interference with time in androgen deprivation therapy recipients relative to matched prostate cancer and cancer-free controls from before the start of androgen deprivation therapy to 12 months later. We also examined demographic, clinical and genetic predictors of the impact of androgen deprivation therapy on hot flash interference.

Materials and Methods: Three groups were examined, including 60 patients with prostate cancer recruited before or within 21 days of starting androgen deprivation therapy, 83 age and education matched patients with prostate cancer treated with prostatectomy only, and 86 age and education matched men with no history of cancer. Participants provided blood samples and completed the Hot Flash Related Daily Interference Scale at baseline as well as 6 and 12 months later.

Results: Androgen deprivation therapy recipients reported increasing hot flash interference with time relative to controls ($p < 0.001$). Group differences were evident at 6 and 12 months (all $p < 0.001$) with androgen deprivation therapy recipients reporting greater hot flash interference than controls. Several genetic polymorphisms were found to predict greater increases in hot flash interference (all $p < 0.01$), including polymorphisms on genes associated with vasoconstriction, immune function, neurotransmission and circadian rhythms. Androgen deprivation therapy recipients who were younger and had a lower body mass index at baseline also showed greater increases in hot flash interference with time (all $p \leq 0.01$).

Conclusions: This study, which is to our knowledge the first to prospectively examine hot flash interference in androgen deprivation therapy recipients, reveals that those with certain genetic polymorphisms, younger age and lower body mass index had greater increases in hot flash interference with time relative to controls.

Key Words: prostatic neoplasms, antiandrogens, hot flashes, quality of life, genetics

As many as 80% of men receiving ADT for prostate cancer experience hot flashes and 27% report hot flashes as the most distressing side effect of ADT.[1] In addition, hot flashes can persist for years after ADT is discontinued.[2] Evidence suggests that concern over hot flashes and other

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side effects can make patients less likely to begin hormonal therapy and lead to its early discontinuation.[3,4] Given the limitations of currently available assessments of hot flashes,[5,6] focus has shifted to examining HFI, the degree to which hot flashes disrupt patient daily activities and quality of life. HFI has been found to be more strongly related to quality of life outcomes (eg sleep quality, anxiety, depression and perceived health state) than the frequency or severity of hot flashes.[7] Thus, research is needed to identify risk factors for HFI during ADT for prostate cancer.

We are unaware of previous studies of potential demographic or clinical predictors of hot flashes or HFI in patients with prostate cancer receiving ADT. However, the literature on patients with breast cancer suggests that differences in hot flash frequency and HFI in patients receiving similar hormonal treatments can be partially explained by demographic and clinical factors. For example, younger patients with breast cancer experience more hot flashes during hormonal therapy.[4] In addition, those with lower BMI report greater HFI than those with greater BMI.[8] Lastly, genetic polymorphisms have been associated with risk of greater hot flashes in patients with breast cancer.[9,10] Although to our knowledge this is unexplored in the cancer literature, genetic polymorphisms in genes associated with hot flashes, such as neurotransmitters,[8] may confer a risk of greater HFI in patients with prostate cancer receiving ADT. These potential risk factors of HFI merit further examination in such patients on ADT.

The purpose of this study was to examine the course of HFI and identify genetic, demographic and clinical moderators of HFI in patients with prostate cancer treated with ADT. We hypothesized that such patients receiving ADT would experience worse HFI than controls who were not androgen deprived, and age, BMI and genetic inheritance would confer a risk of greater HFI in these men.

MATERIALS AND METHODS

Participants

Participants were recruited as part of a larger study examining the impact of ADT on cognitive function and quality of life. Details regarding eligibility criteria, recruitment procedure and matching criteria were described previously.[11] Briefly, all participants were required to be older than 18 years, be able to speak and read English, have a greater than sixth grade education, have no history of stroke and not demonstrate impaired mental status based on screening according to a SPMSQ (Short Portable Mental Status Questionnaire) score of less than 3. Patients with prostate cancer receiving ADT were also required to be scheduled to start ADT or have started ADT within the last month for nonmetastatic or asymptomatic metastatic prostate cancer, be scheduled to received ADT for at least 6 months, have not received treatment for any other cancers in the previous 12 months, have no history of brain cancer or previous cranial irradiation and no treatment with ADT in the previous 12 months or an antiandrogen agent in the previous 6 months. Patients with prostate cancer not treated with ADT were also required to be diagnosed with nonmetastatic prostate cancer, have no history of other cancers except nonmelanoma skin cancer, have undergone prostatectomy but no other form of prostate cancer treatment, have no history of recurrent disease since undergoing prostatectomy and not be receiving testosterone supplementation. Matched men with no cancer history were also required to have no history of any form of cancer except nonmelanoma skin cancer and not be receiving testosterone supplementation.

ADT group participants were matched to participants with no ADT on time since diagnosis (within 6 months). The no ADT and no cancer group participants were recruited to be matched to ADT participants on age (within 5 years) and educational level (12 years or less, 13 to 16, or 17 or greater). This study was approved by the institutional review board at University of South Florida.

Procedure

Baseline assessments were completed by ADT participants before or within 21 days of starting ADT, and 6 and 12 months later. The no ADT and no cancer participants were assessed at similar intervals. Participants provided blood samples at baseline. Supplementary figures 1 to 3 (http://jurology.com/) show information about participant flow.

Measures

Age, marital status, education, race and ethnicity were assessed at baseline via self-report. Medical comorbidities were assessed at baseline using a self-report version of the Charlson comorbidity index.[12] Gleason score was determined via medical chart review. Height and weight were evaluated at baseline and BMI was calculated using standard scoring.[13]

Self-reported daily HFI was assessed at each time point using HFRDIS (Hot Flash Related Daily Interference Scale),[14] a valid and reliable measure used in prior prostate cancer studies.[14–16] This scale assesses the impact of hot flashes on daily activities (eg leisure activities and sleep) as well as on overall quality of life. Scores range from 0 to 100 with higher scores indicating greater interference.

SNP Selection and Genotyping

A literature search identified SNPs with evidence of associations with cognitive impairment, depression, fatigue or circadian rhythms. Preference was given to SNPs in coding regions or known transcription factor binding sites that were identified as nonsynonymous mutations and with a minor allele frequency of 0.20 or greater in the HapMap (http://hapmap.ncbi.nlm.nih.gov/citinghapmap.html.en) CEU (Utah residents with ancestry from northern and western Europe) population.[17] Of 494 SNPs initially identified 384 were retained after an iterative custom panel design process. Although not included due to a priori hypotheses of associations with HFI, many