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

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Abstract

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

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

Results—ADT recipients reported increasing HFI over time relative to controls ($p < .001$). Group differences were evident at 6 and 12 months ($ps < .001$), with ADT recipients reporting greater HFI than controls. Several genetic polymorphisms were found to predict greater increases in HFI ($ps < .01$), including polymorphisms on genes associated with vasoconstriction, immune function, neurotransmission, and circadian rhythms. ADT recipients who were younger and had lower body mass index at baseline also exhibited greater increases in HFI over time ($ps < .01$).

Conclusions—This study, the first to prospectively examine HFI in ADT recipients, found that those with certain genetic polymorphisms, younger age, and lower BMI had greater increases in HFI over time relative to controls.

Keywords

Prostate Cancer; Antiandrogens; Hot Flashes; Quality of Life; Genetics

Introduction

As many as 80% of men receiving androgen deprivation therapy (ADT) for prostate cancer experience hot flashes and 27% reported 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 side-effects can make patients less likely to begin hormonal therapy and can lead to its early discontinuation.^{3, 4} Given the limitations of currently-available assessments of hot flashes,^{5, 6} focus has shifted to examining hot flash interference (HFI), the degree to which hot flashes disrupt patients daily activities and quality of life. HFI has been found to be more strongly related to quality of life outcomes (e.g., sleep quality, anxiety, depression, 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 examining potential demographic or clinical predictors of hot flashes or HFI in prostate cancer patients receiving ADT. However, the literature in breast cancer patients 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 breast cancer patients experience more hot flashes during hormonal therapy.⁴ In addition, breast cancer patients with lower body mass index (BMI) report greater HFI than those with greater BMI.⁸ Lastly, genetic polymorphisms have been associated with risk of greater hot flashes in breast cancer patients.^{9, 10} Although unexplored in the cancer literature, genetic polymorphisms in genes associated with hot flashes, such as neurotransmitters,⁸ may confer risk of greater HFI among prostate cancer patients receiving ADT. These potential risk factors of HFI merit further examination in prostate cancer patients receiving ADT.

The purpose of this study is to examine the course of HFI as well as to identify genetic, demographic, and clinical moderators of HFI in prostate cancer patients treated with ADT. We hypothesized that prostate cancer patients receiving ADT would experience worse HFI than controls who were not androgen-deprived and that age, body mass index (BMI), and genetic inheritance would confer 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 are described elsewhere.¹¹ Briefly, all participants were required to: be 18 years of age, be able to speak and read English, have sixth grade education, have no history of stroke, and not demonstrate impaired mental status based on

screening (Short Portable Mental Status Exam score < 3). Prostate cancer patients receiving ADT (ADT+ group) were also required to be scheduled to start ADT or have started ADT within the past month for non-metastatic or asymptomatic metastatic prostate cancer, be scheduled to receive 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 have not been treated with ADT in the previous 12 months or an anti-androgen agent in the previous 6 months. Prostate cancer patients not treated with ADT (ADT- group) were also required to: be diagnosed with non-metastatic prostate cancer, have no history of other cancers except non-melanoma skin cancer, have undergone prostatectomy but no other forms of prostate cancer treatment, have no history of recurrent disease since undergoing prostatectomy, and not be receiving testosterone supplementation. Men with no cancer (CA- group) were also required to have no history of any form of cancer except non-melanoma skin cancer and not be receiving testosterone supplementation. ADT- group participants were matched to ADT+ participants on time since diagnosis (within 6 months); ADT- and CA- group participants were recruited to be matched to ADT+ participants on age (within 5 years) and educational level (12 years, 13–16 years, or 17 years). This study was approved by the Institutional Review Board at the 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. ADT- and CA- participants were assessed at similar intervals. Participants provided blood samples at baseline. See Supplementary Figures 1 – 3 for 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 assessed via medical chart review. Height and weight were assessed at baseline; BMI was calculated using standard scoring.¹³

Self-reported daily HFI was assessed at each time point using the 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 (e.g., leisure activities, sleep) as well as overall quality of life. Scores range from 0 – 100; higher scores indicate greater interference.

Single Nucleotide Polymorphism (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, identified as non-synonymous mutations, and with minor allele frequency > .20 in the HapMap CEU 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 SNPs were on genes with plausible implications for hot flashes.

DNA was extracted from blood obtained using Gentra Puregene tissue kits (Valencia, CA) according to the manufacturer's instructions and genotyped using the Illumina GoldenGate™ assay (Illumina, San Diego, CA). Genotypes were determined using the BeadStudio algorithm by the Moffitt Molecular Genomics Core.

Statistical Analyses

Analyses were restricted to the 60 ADT+, 83 ADT–, and 86 CA– participants who completed the baseline assessment and at least one follow-up assessment. Those deemed ineligible because data were not available from baseline and/or one follow-up assessment ($n=56$) did not differ from those deemed eligible on demographic or clinical variables within any group ($ps \geq .28$). Potential covariates that differed between groups at $p < .10$ were included in all multivariate analyses.

Mixed model analyses, allow for the use of all available data at each time point,¹⁸ were conducted on changes in HFI over time using PROC MIXED in SAS, Version 9.4 (Cary, NC).¹⁹ A two-sided alpha value of .05 was used as the criterion for statistical significance. Effect sizes were calculated using Cohen's d .²⁰

Mixed model analyses were conducted with JMP Genomics²¹ to model change in HFI from baseline to 12 months as a function of group status and genotype. A false discovery rate of $q < .05$ ²² was used to control for multiple comparisons. Additive models were examined using only those SNPs at Hardy-Weinberg equilibrium in the cancer-free group, with a minor allele frequency in the current sample $\geq 1\%$, and with missing genotype data for $\leq 20\%$ of participants in the current sample. Genetic analyses used data from only participants who self-identified as white because ancestry informative markers were not measured and few participants identified as non-white.

Exploratory linear regression analyses were conducted using the PROCESS macro²³ to identify potential moderators and mediators of the impact of ADT on 12-month HFI while controlling for baseline HFI. The Johnson-Neyman technique²⁴ was used to calculate the region of significance, the value of the moderator above which receipt of ADT was no longer significantly associated with HFI.

Results

Demographic & Medical Characteristics

See Table 1 for demographic and clinical characteristics. The ADT+ group reported more medical comorbidities and had higher Gleason scores than the ADT– group ($ps < .06$). The ADT+ group also reported fewer years of education, was less likely to be married, and was less likely to be white than the ADT– and CA– groups ($ps \geq .08$). Thus, medical comorbidities, education, marital status, and race were included as covariates in subsequent analyses. Because ADT treatment was prescribed for more advanced disease, Gleason score was not entered as a covariate.

In order to increase statistical power and reduce the number of statistical tests performed, preliminary analyses were conducted to determine whether the ADT– and CA– groups

could be combined. Because HFI did not differ between the ADT– and CA– groups at any time point ($p = .11$) and there was no group by time interaction ($p = .42$), these groups were combined into a single control group (see Supplementary Figure 4).

Change Over Time in Hot Flash Interference

Figure 1 presents adjusted group means for HFI. A significant group by time interaction was observed when comparing HFI between the ADT+ group and the control group ($p < .001$). No group differences were evident at baseline ($p = .10$); however the ADT+ group demonstrated greater HFI than controls at 6 months ($p < .001$; $d = 1.40$) and 12 months ($p < .001$, $d = 1.78$). Analyses within groups indicated that the HFI worsened over time in the ADT + group ($p < .001$) but did not significantly change in the control group ($p = .14$).

Predictors of Change in Hot Flash Interference

Genetic data were analyzed in the 48 ADT+ group participants and 158 control group participants who self-identified as white and had evaluable genetic data. Of the 384 SNPs measured, 31 were excluded based on quality control parameters described above. A total of 353 variants were analyzed, and 102 were significantly associated ($p < .05$) with residualized change in HFI from baseline to 12 months using the additive model. Of these, 101 SNPs also met the cutoff of $q < .05$ (see Supplementary Table 1). Plots of group by SNP interactions are presented in Figure 2 for selected SNPs. ADT+ group participants with variants in the following SNPs reported greater increases in HFI over time relative to ADT+ group participants with homozygous or wild type genotype and all control group participants: rs2069777 in *IL2*, rs5744256 in *IL18*, rs9534505 in *HTR2A*, and rs7209436 in *CRHR1*. ADT+ group participants with wild type genotypes for rs11932595 in *CLOCK* and rs265981 in *DRD1* reported greater increases in HFI over time relative to ADT+ group participants with homozygous mutant or heterozygous genotype as well as all control group participants.

Regression analyses examined potential baseline moderators of the impact of ADT on HFI. Age and body mass index significantly moderated the impact of ADT on HFI ($p = .01$), such that the impact of ADT on HFI was greatest among men who were younger and had lower BMI at baseline (see Figure 3). Additional analyses indicated that ADT did not have a statistically significant impact on HFI at 12 months in men aged ≥ 82 or those with a BMI of ≥ 36 kg/m squared.

Discussion

This was the first prospective study to examine the impact of ADT on HFI in prostate cancer patients over the year following treatment initiation and the first to examine moderators of the impact of ADT on HFI in prostate cancer patients. Results confirmed our hypothesis that men receiving ADT for prostate cancer would report greater HFI over time than controls

¹Among participants in the ADT+ group, 55 completed the baseline assessment on or before the day of their first ADT injection; 5 were assessed within 21 days after their first ADT injection ($M = 12$ days, $SD = 6.59$). Significant findings comparing groups on change over time in interference from hot flashes remained significant regardless of whether these 5 participants were included in the analyses.

who were not androgen-deprived and that age, BMI, and genetic inheritance would confer risk of greater HFI over time.

ADT recipients reported significantly worse HFI at 6 months and 12 months, with group differences at follow-up assessments reflecting large effects ($d = 1.40$).²⁰ SNPs that were significantly associated with change in HFI included polymorphisms on genes associated with immune function (*i.e.*, *IL2*, *IL18*, *CR1*, *IL1RN*, *VIPR2*), neurotransmission (*i.e.*, *HTR2A*, *DRD1*, *IDO2*), vasoconstriction (*i.e.*, *ACE*), and circadian rhythms (*i.e.*, *CLOCK*, *PER2*, *TIMELESS*, *CRY1*). Many are on genes with plausible biological mechanisms impacting hot flashes. For example, *ACE* codes for the angiotensin converting enzyme which plays an important role in vasoconstriction. Constriction and dilation of blood vessels is the primary method by which core body temperature is adjusted.²⁵ Findings for other SNPs are in line with previous studies showing associations between neurotransmission and inflammation²⁶ as well as between inflammation and hot flashes.^{27, 28} The potential role of mutations on genes associated with vasoconstriction, neurotransmission, and immune function in moderating the impact of ADT on HFI merits further investigation.

With regard to demographic and clinical moderators, the impact of ADT on HFI was weaker among older patients. The impact of ADT on HFI was also weaker among men with higher BMI at baseline. Findings regarding the moderating impact of age and BMI on HFI are in line with studies in the breast cancer literature showing that, among women treated with hormonal therapy, younger patients and those with lower BMI experience more hot flashes.^{4, 8}

This study possesses limitations, including that the potential impact of testosterone and estradiol levels were not examined. Because anxiety was not assessed, this study could not determine whether anxiety was associated with HFI, as has been found among breast cancer patients.²⁹ Lastly, this study could not determine whether HFI diminishes after 12 months.

Conclusions

As hypothesized, men receiving ADT for prostate cancer experienced greater HFI than a control group of matched men with prostate cancer not treated with ADT and matched men with no history of cancer. In addition, ADT recipients with certain genetic polymorphisms as well as those who were younger and had lower BMI at baseline experienced even greater HFI. The clinical implications of these findings are important and are relevant to discussions of the risks and benefits of ADT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ADT	androgen deprivation therapy
HFI	hot flash interference
BMI	body mass index
ADT+	group of prostate cancer patients treated with ADT
ADT–	group of matched prostate cancer patients not treated with ADT
CA–	group of matched men with no history of cancer
SNP	single nucleotide polymorphism

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Figure 1.

Adjusted group means for hot flash interference.

Note: No group differences at baseline ($p = .10$). Group differences at 6 months ($p < .001$) and 12 months ($p < .001$) reflected large effect sizes (Cohen's $d = 1.40$). HFI increased over time in ADT recipients ($p < .001$) but did not change in controls ($p = .14$).

Figure 2.

Unadjusted means of hot flash interference by group and genotype.

Note: SNPs on genes associated with immune function (A and B), neurotransmission (C and D), and circadian rhythms (E). For some SNPs, HFI varied significantly as a function of genotype in ADT recipients but not in controls.

Figure 3.

Demographic and clinical moderators of hot flash interference.

Note: The impact of ADT on HFI was greatest among men who were younger and had lower BMI at baseline ($p < .01$). The impact of ADT on HFI was no longer statistically significant at 12 months in men aged ≥ 82 or with BMI ≥ 36 kg/m² at baseline

Table 1

Demographic and Clinical Characteristics of the Sample

Characteristic	ADT+ (n = 60)	ADT- (n = 83)	CA- (n = 86)	ADT+ vs. ADT- <i>p</i>	ADT+ vs. CA- <i>p</i>
Age, years					
Mean	68.10	68.05	69.08	.97	.49
SD	8.75	7.29	8.06		
Years of Education					
Mean	14.00	14.78	14.90	.08	.03
SD	2.44	2.71	2.46		
Body mass index, kg/m ²					
Mean	28.22	29.53	29.72	.10	.10
SD	4.21	4.32	5.24		
Comorbidity index score					
Mean	2.83	2.45	2.69	.01	.41
SD	1.04	0.90	1.08		
Characteristic	No. (%)	No. (%)	No. (%)	<i>p</i>	<i>p</i>
Marital Status					
Married	37 (62)	64 (77)	75 (87)	.05	<.001
Not married	23 (38)	19 (23)	11 (13)		
Race					
White	51 (85)	79 (95)	83 (97)	.04	.01
Nonwhite	9 (15)	4 (5)	3 (3)		
Gleason score					
4–6	8 (13)	40 (48)	-	<.001	-
7	22 (37)	37 (45)	-		

	ADT+ (n = 60)	ADT- (n = 83)	CA- (n = 86)	ADT+ vs. ADT- ADT+ vs. CA-	ADT+ vs. CA-
8	19 (32)	2 (2)	-		
9-10	7 (12)	0 (0)	-		
Missing	4 (6)	4 (5)	-		

Note. N = 239. SD = standard deviation. p values calculated using χ^2 for categorical variables and t-tests for continuous variables. Missing levels were excluded from calculation of p values.