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Genetic predictors to acupuncture response for hot flashes: An exploratory study of breast cancer survivors

Sally A. D. Romero, PhD MPH[1,2], **Q. Susan Li, MS**[1], **Irene Orlow, PhD**[1], **Mithat Gonen, PhD**[1], **H. Irene Su, MD MSCE**[2], **Jun J. Mao, MD MSCE**[1]

[1]Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065

[2]UC San Diego Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093

Abstract

Objective: Since hot flashes are a common symptom experienced by women with breast cancer, we sought to explore genetic predictors associated with response to acupuncture for the treatment of hot flashes.

Methods: Using data from our completed randomized controlled trial (Clinicaltrials.gov identifier: NCT01005108) on hot flashes among breast cancer survivors who provided biomarker collection (N=108), we extracted and assayed DNA for single nucleotide polymorphisms (SNPs) in genes involved in neuro-transmission, thermo-regulation, and inflammation (*ADORA1*, *COMT*, *TCL1A*, and *TRPV1*). For our primary outcome we classified individuals with a 50% or more reduction in their hot flash composite score at the end of treatment as responders. We used Fisher's exact test to identify individual and combined SNPs associated with treatment response.

Results: Among women (N=57) who received acupuncture treatment (electro- or sham), we found that women who were carriers of at least one of these six genotypes (*ADORA1* rs41264025-GA or rs16851029-GG or rs12744240-GT, *COMT* rs6269-GA, *TCL1A* rs2369049-GG, and *TRPV1* rs8065080-TT) were more likely to respond to acupuncture for hot flashes than non-carriers (70.3% vs. 37.5%, p=0.035). These six genotypes were not associated with response in women (N=51) who received pharmacological hot flash treatment (gabapentin or placebo pill (37.5% vs. 37.5%, p=1.0).

Conclusions: In this exploratory, proof of concept study, we identified six genotypes that may predict response to acupuncture for hot flashes in breast cancer survivors. If confirmed by future studies, these findings may inform the development of personalized acupuncture for managing hot flashes.

Corresponding author: Jun J. Mao, MD, MSCE, Memorial Sloan Kettering Cancer Center, Bendheim Integrative Medicine Center, 1429 First Avenue, New York, NY 10021, Phone: 646-888-0866; Fax: 212-717-3185; maoj@mskcc.org. Corresponding author for peer review: Sally A. D. Romero, PHD, MPH, University of California San Diego, Moores Cancer Center, 3855 Health Sciences Drive, La Jolla, CA 92093, saromero@ucsd.edu.

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Keywords

breast neoplasm; hot flashes; genetics; acupuncture

Introduction

Hot flashes are one of the most common and distressing symptoms experienced by up to 73% of breast cancer survivors after cancer treatment.[1–4] Hot flashes result when a thermo-regulatory problem occurs in the body, usually induced by a reduction in estrogen levels.[5,6] Some cancer treatments, such as surgery, chemotherapy, and anti-estrogen therapies, disrupt estrogen synthesis and activity, which can result in severe hot flashes.[1,7] Thus, having effective treatment options for hot flashes is important for improving the survivorship experience of breast cancer survivors.

Acupuncture, a non-pharmacological therapy, involves penetrating the skin with thin, solid, metallic needles that are manipulated by hand or electrical stimulation.[8] It is used by cancer survivors at a higher rate than the general population[9] and is considered safe with few side effects (e.g. needling pain, bruising).[10] In a randomized controlled trial (RCT) with breast cancer survivors (N=190), Lesi et al. found that acupuncture along with self-care was better than self-care alone for hot flashes and quality of life.[11] Findings from our completed RCT (N=120 breast cancer survivors) showed that acupuncture produced a reduction in hot flashes similar to gabapentin but with fewer side effects; in addition, the effects appeared to persist over time.[12]

Growing research has been dedicated to finding genetic biomarkers to improve cancer treatment-related symptoms.[13] Given the potential of precision medicine for cancer treatment-related symptoms, the objective of this proof of concept study was to explore the association between selected candidate single nucleotide polymorphisms (SNPs) in genes involved in neuro-transmission [Catechol-O-methyltransferase (*COMT*)[14,15] and Adenosine A1 Receptors (*ADORA1*)[16–18]] thermo-regulation [Transient Receptor Potential Cation Channel Subfamily V Member 1 (*TRPV1*)[19,20]], and inflammation [T-cell leukemia 1A (*TCL1A*)[21,22]] pathways and response to acupuncture for the treatment of hot flashes among breast cancer survivors. We hypothesized that these selected candidate SNPs would be associated with a positive response to acupuncture treatment for hot flashes.

Methods

Study population

We used data from our completed RCT on hot flashes among breast cancer survivors (Clinicaltrials.gov identifier: NCT01005108).[12] The full details of the completed RCT and the primary findings have been previously published.[12] In brief, women with a history of stage I-III breast cancer, who reported at least two hot flashes per day for the previous seven days and had hot flashes for at least one month prior to enrollment, were recruited from the Abramson Cancer Center of the Hospital of the University of Pennsylvania (Philadelphia, PA). One hundred and twenty women were randomized to four arms (electro-acupuncture,

sham acupuncture, gabapentin, and placebo pill). One hundred and eight women (90% of total) provided a peripheral blood sample, and of these, 84 (78%) women were White. Samples were banked at −80°C for genetic and biomarker analysis. For the exploratory analyses described in this paper, women were grouped into two arms: 1) acupuncture (electro- and sham) (N=57) and 2) pill (gabapentin and placebo) (N=51) due to the small sample size in each of the four arms (N range: 25 to 29). The Institutional Review Board of the University of Pennsylvania approved the study protocol.

Primary Outcome

The primary outcome was a 50% or more reduction in the weekly average hot flash composite score as measured by the Daily Hot Flash Diary. Each participant recorded the number and severity of daily hot flashes starting from Baseline until Week 12 and again for one week at Week 24. The composite score for each day was calculated by multiplying the number of mild, moderate, severe, or very severe hot flashes by 1, 2, 3, or 4, respectively, and adding the values.[23] Based on previous research, we developed a dichotomous outcome that considered those individuals with a 50% or more reduction in their hot flash composite score at the end of treatment to be responders.[24,25]

SNP Genotyping and Selection

Based on existing literature of polymorphisms in genes that have been found to play a role in the mechanism of acupuncture, we selected 18 candidate SNPs in genes involved in neuro-transmission,[14–18] thermo-regulation,[19,20] and inflammation[21,22] pathways. Participant DNA was extracted from buffy coat specimens using the Qiagen QiaAmp 96 DNA Blood Kit (Valencia, CA). SNPs were genotyped using the SNPlex or the OpenArray platform from Applied Biosystems (Foster City, CA). Given the small sample size in each arm, we selected SNPs that had at least a greater than 15% difference in treatment responders (the primary outcome) between the allele groups rather than relying on a p-value.

Statistical Analysis

Descriptive statistics were conducted to obtain the N (%) of participants having the specific SNP in each treatment group as well as the N (%) of participants who were classified as treatment responders. We used Fisher’s exact test to identify the individual and combined SNPs associated with response to treatment for hot flashes. Data analyses were conducted using STATA 15.0 for Windows (STATA Corporation, College Station, TX).

Results

Genotyping failure rates were <1.8%. All SNP distributions satisfied Hardy-Weinberg proportions and were consistent with reported reference SNP frequencies (data not shown). If the frequency for one of the genotypes was <5% of the population, we collapsed the SNPs genotypes into two categories. As shown in Table 1, six SNPs out of the initial 18 candidate SNPs had a difference of at least >15% in treatment responders between the allele groups: *ADORA1* rs41264025-GA vs. GG; *ADORA1* rs16851029-GG vs. TT/GT; *ADORA1* rs12744240-GT vs. GG; *COMT* rs6269-GA vs. AA/GG; *TCL1A* rs2369049-GG vs. AA/GG; and *TRPV1* rs8065080-TT vs. CT/CC.

Since the proportion of women who were carriers of each SNP ranged from 1 to 52% (MAF ranges from 0.024 to 0.488), we classified women who were carriers of at least one of the six SNPs listed above as carriers of a potentially "responsive genotype". Seventy percent of women in our population were carriers of this responsive genotype. Among women (N=57) who received acupuncture treatment, 70.2% were carriers, and among those who received pharmacological treatment (N=51), 84.3% were carriers.

Figure 1 illustrates the response to treatment (acupuncture or pill) by carrier status of the responsive genotype. Among women who received acupuncture treatment, we found that women who were carriers of at least one of these six SNPs (*ADORA1* rs41264025-GA or rs16851029-GG or rs12744240-GT, *COMT* rs6269-GA, *TCL1A* rs2369049-GG, and *TRPV1* rs8065080-TT) were more likely to respond to acupuncture for hot flashes than non-carriers (70.3% vs. 37.5%, p=0.035). To ensure these genotypes were not associated with response to any therapy or enrollment in a clinical trial, we repeated the analyses among women who received pharmacological hot flash treatment and did not find any evidence for predicting response (37.5% vs. 37.5%, p=1.0).

Discussion

Considering the prevalence, significance, and impact of hot flashes among breast cancer survivors,[1–4] treatment options that apply a precision medicine framework to optimize hot flash management are needed. In this exploratory, proof of concept study, we identified six SNPs (*ADORA1* rs41264025-GA or rs16851029-GG or rs12744240-GT, *COMT* rs6269-GA, *TCL1A* rs2369049-GG, and *TRPV* rs8065080-TT) present in 70% of our population that may predict response to acupuncture for hot flashes in breast cancer survivors.

While we were not able to identify literature on genetic predictors associated with acupuncture response to hot flashes, previous research has demonstrated that polymorphisms in genes involved in neuro-transmission,[14–18] thermo-regulation,[19,20] and inflammation[21,22] have been found to play a role in the mechanism of acupuncture. In particular, *COMT* is involved in neuro-transmission by regulating dopamine catabolism and playing a key role in prefrontal cortex processes associated with the placebo effect such as reward, pain, memory, and learning.[14,15] We recently found that a polymorphism in *COMT* was associated with response to acupuncture for the management of pain symptoms in women with breast cancer.[26]

Additionally, *ADORA1* is a neuromodulator with inhibitory function, such as anti-nociceptive properties.[18] From previous animal model research, acupuncture has been shown to activate *ADORA1* pathways through increased adenosine concentrations at acupoints, which may mediate the local anti-nociceptive effects and improve neuropathic pain.[16,17] Further, the effect of acupuncture has been found to be influenced by the activation of mast cells in acupoints via *TRPV1* and *ADORA1* pathways.[27–29] Additionally, *TRPV1* plays a role in thermo-regulation; mice exposed to a *TRPV1* agonist exhibit vasomotor symptoms-like responses, such as a drop in core body temperature and cold-seeking behavior.[20] These findings support that the underlying biological mechanisms

associated with acupuncture's effect though *ADORA1* and *TRPV1* pathways may explain the response to acupuncture for hot flashes.

Further, *TCL1A* signals influence proinflammatory cytokines and chemokines through its interactions with Akt kinase and its involvement with cell proliferation, stabilizing mitochondrial membrane potential, and promoting cell survival.[22,30] Previous studies have identified four SNPs in high linkage disequilibrium and close to *TCL1A*, including rs2369049, that are associated with estradiol-induced *TCL1A* expression, musculoskeletal adverse events in women treated with AIs, and IL-17 production.[21,22,31] Further, Bao et al. found that acupuncture appeared to reduce peripheral circulating IL-17 in breast cancer survivors.[32] Our findings, in line with these previous studies, suggest biological plausibility that SNP rs2369049 may be involved in the mechanism of acupuncture response via inflammatory pathways.

Given the multiple comparison and exploratory nature of these post-hoc analyses, our findings are primarily useful for hypothesis generation and may be at risk for false positives. However, we did not see any association between the potentially responsive genotype and response to treatment by those in the pill group suggesting that the responsive genotype may be unique to the acupuncture process. Due to the small sample size, we had to combine the electro-acupuncture and sham acupuncture into one group. As acupuncture is a complex intervention involving both the process of delivery and needling specificity, future research may help uncover a genetic signature that predicts response to different types of acupuncture.

Conclusions

Despite this study's limitations, our findings in this exploratory, proof of concept study suggest that six genotypes related to neuro-transmission, thermo-regulation, and inflammation pathways may predict response to acupuncture for the treatment of hot flashes. Future validation of these findings in an independent study with an adequate sample size is warranted and has the potential to personalize the integration of acupuncture based on host genetics to optimize hot flash management.

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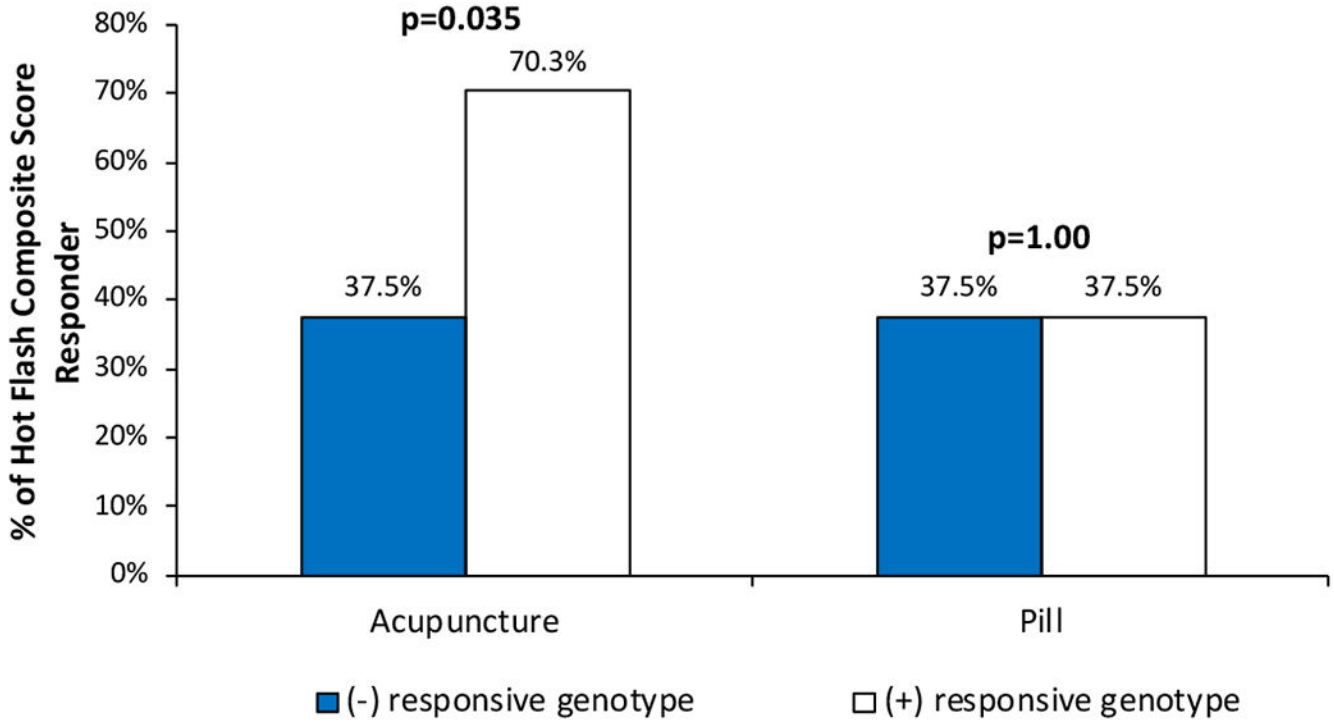

Figure 1.

Response to hot flash treatment by presence or absence of the potentially "responsive genotype" (carrier of at least one of these six SNPs: *ADORA1* rs41264025-GA or rs16851029-GG or rs12744240-GT, *COMT* rs6269-GA, *TCL1A* rs2369049-GG, and *TRPV1* rs8065080-TT)

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Table 1:

Association between individual single nucleotide polymorphisms and response to hot flash treatment

Gene	Polymorphism[a]	Functional Consequence	Treatment Type: Acupuncture (N=57)			Treatment Type: Pill (N= 51)		
			Participants N (%)	Responders N (%)	p-value[b]	Participants N (%)	Responders N (%)	p-value[b]
ADORA1[c]	**rs41264025**	Exon 3′-UTR[g] variant			0.14			0.28
	GG		52 (91)	27 (56)		42 (89)	16 (40)	
	GA		5 (9)	5 (100)		5 (11)	0 (0)	
	rs16851029	Exon 3′-UTR[g] variant			1.00			NA
	TT/GT		55 (98)	30 (59)		48 (100)	17 (37)	
	GG		1 (2)	1 (100)		0 (0)	0 (0)	
	rs12744240	Exon 3”-UTR[g] variant			0.13			0.71
	GG		48 (84)	25 (56)		40 (78)	14 (36)	
	GT		9 (16)	7 (88)		11 (22)	4 (44)	
COMT[d]	**rs6269**	Intron variant			0.17			0.15
	AA/GG		30 (53)	15 (52)		21 (42)	10 (50)	
	GA		27 (47)	17 (71)		29 (58)	8 (28)	
TCL1A[e]	**rs2369049**	Intron variant			0.38			0.62
	AA/AG		51 (89)	27 (57)		43 (88)	15 (36)	
	GG		6 (11)	5 (83)		6 (12)	2 (50)	
TRPV1[f]	**rs8065080**	Missense variant			0.26			0.37
	TT		21 (38)	14 (70)		20 (42)	9 (45)	
	CT/CC		35 (62)	17 (53)		28 (58)	8 (31)	

a. rs, reference sequence

b. Fisher’s Exact Test. Outcome is dichotomized hot flash composite score responder (>50% reduction in hot flashes) at end of treatment.

c. *ADORA1,* Adenosine A1 Receptors

d. *COMT,* Catechol-O-methyltransferase

e. *TCL1A,* T-cell leukemia 1A

f. *TRPV1,* Transient Receptor Potential Cation Channel Subfamily V Member 1

g. 3’-UTR, three prime untranslated region