Perturbed inflammatory, regulatory, and neurodegeneration signaling pathways are associated with trait anxiety in cancer survivors

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Introduction

Trait anxiety is a common psychosocial symptom experienced by cancer survivors. However, little is known about its contributing biological mechanisms or how they may differ in survivors as compared to the general population. The purposes of this study were to (1) evaluate for perturbed biological pathways associated with trait anxiety severity in cancer survivors, (2) evaluate for perturbed biological pathways associated with trait anxiety severity in the general population, and (3) identify common and distinct perturbed pathways across these cohorts.

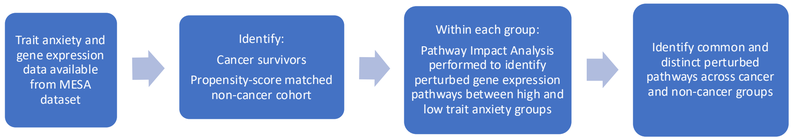

Figure 1: Methods overview

Methods

Patients and settings

Participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a prospective longitudinal study, were used in this analysis. Eligible MESA participants are between the ages of 45 and 84 at enumeration, who are African-American, Chinese-American, Caucasian, or Hispanic, and who do not meet any of the exclusion criteria. Exclusion criteria include active treatment for cancer and serious medical conditions. Gene expression and trait anxiety data were available for 1,102 participants at baseline. Survivorship was defined as a self-report of a history of a cancer diagnosis. Access to dbGaP datasets for this study was approved in project request #39341.

Trait Anxiety

Trait anxiety was assessed at baseline using ten questions from the Spielberger Trait Anxiety Scale. Participants were split into low (<3rd quartile) and high (≥ 3rd quartile) trait anxiety groups.

Propensity-Score Matching

Using propensity-score matching (PSM), we identified a cohort in the general population group who did not report previous cancer diagnoses matched in sociodemographic characteristics to the cancer survivors. 1:3 matching on propensity scores using the optimal pair-matching algorithm was used. In the PSM cohort, there were N = 74 cancer survivors and N = 222 non-cancer controls. PSM was evaluated with 7 demographic and 1 clinical characteristic (marked '^' in Table 1).

Demographic and Clinical Characteristics

Characteristics included age, anti-depressant use, site, race/ethnicity, diabetic and hypertensive status, employment, cancer diagnosis, BMI, education level, marital status, and income. In the cancer survivor cohort, gender significantly differed between low and high trait anxiety groups. In the background cohort, marital status significantly differed between low and high trait anxiety groups.

Data Analysis

Differential gene expression was evaluated between low and high trait anxiety groups within each cohort. Differential expression was quantified using empirical Bayes models using edgeR. These analyses were adjusted for significant phenotypic characteristics (i.e., gender for the survivor cohort and marital status for the PSM matched cohort). The models included surrogate variables not associated with trait anxiety to adjust for variation due to unmeasured sources.

Pathway Impact Analysis (PIA) was used to interpret the gene expression results as it related to trait anxiety mechanisms. The PIA included the results of differential gene expression analyses for all genes to determine the probability of pathway perturbations.

A total of 138 signaling pathways were evaluated using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database. The results were evaluated for common and distinct pathways associated with trait anxiety across the survivor and general population samples.

Results

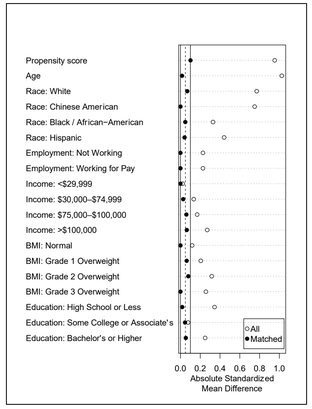

Figure 2: Loveplot depicting absolute standardized mean differences for covariates between the entire participant cohort and the matched cohort.

Characteristics	Low trait anxiety (N = 63)	High trait anxiety (N = 11)	p-value	Test Statistic
Demographic Characteristics				
^Age (median, IQR)	69 (10)	66 (13)	0.461	t = 0.81
^Gender, n (%):				
female	27 (43%)	9 (82%)	0.023	OR = 0.17
male	36 (57%)	2 (18%)		
Site, n (%)				
WFU	9 (14%)	1 (9%)	0.759	$x^2 = 2.91$
COL	13 (21%)	4 (36%)		
JHU	17 (27%)	4 (36%)		
UMN	18 (29%)	2 (18%)		
NWU	4 (6%)	0 (0%)		
UCLA	2 (3%)	0 (0%)		
^Race/Ethnicity, n (%)				
White, Caucasian	43 (68%)	9 (82%)	0.823	$x^2 = 0.93$
Chinese American	1 (2%)	0 (0%)		
Black, African-American	11 (17%)	1 (9%)		
Hispanic	8 (13%)	1 (9%)		
^Employment, n (%)				
Not working	31 (49%)	5 (45%)	1	$x^2 = 0.05$
Working for pay	32 (51%)	6 (55%)		
^Marital status, n (%)				
Married	43 (68%)	5 (45%)	0.172	$x^2 = 3.54$
Widowed/divorced/separated	17 (27%)	4 (36%)		
Never married	3 (5%)	2 (18%)		
^Household income, n (%)				
<$29,999	21 (33%)	3 (27%)	0.653	$x^2 = 1.71$
$30,000 - $74,999	23 (37%)	6 (55%)		
$75,000 - $100,000	4 (6%)	0 (0%)		
>$100,000	15 (24%)	2 (18%)		
^Education, n (%)				
High school or less	4 (6%)	1 (9%)	0.307	$x^2 = 2.68$
Some college, technical, or associate's degree	28 (44%)	2 (18%)		
Bachelor's degree or more	31 (49%)	8 (73%)		

Characteristics	Low trait anxiety (N = 63)	High trait anxiety (N = 11)	p-value	Test Statistic
Clinical Characteristics				
Tricyclic anti-depressants, n (%):				
No	61 (97%)	10 (91%)	0.387	OR = 2.99
Yes	2 (3%)	1 (9%)		
Diabetes, n (%)				
Normal	48 (76%)	8 (73%)	0.097	$x^2 = 7.30$
IFG	11 (17%)	1 (9%)		
Untreated diabetes	1 (2%)	2 (18%)		
Treated diabetes	3 (5%)	0 (0%)		
Cancer Diagnosis, n (%)				
Breast only	8 (13%)	1 (9%)	0.728	$x^2 = 2.44$
Colon only	5 (8%)	0 (0%)		
NM Skin only	17 (27%)	4 (36%)		
Other, Multiple, or Not Specified	28 (44%)	4 (36%)		
Prostate Only	5 (8%)	2 (18%)		
^BMI, n (%)				
Normal	18 (29%)	4 (36%)	0.693	$x^2 = 1.25$
Grade 1 Overweight	30 (48%)	6 (55%)		
Grade 2 Overweight	14 (22%)	1 (9%)		
Grade 3 Overweight	1 (2%)	0 (0%)		
Hypertension, n (%)				
None	47 (75%)	8 (73%)	1	$x^2 = 0.02$
Hypertension	16 (25%)	3 (27%)		

Table 1: Demographic and clinical characteristic differences between cancer survivors experiencing low and high trait anxiety

A total of 40 pathways were significantly perturbed between high and low trait anxiety groups among cancer survivors (all FDR < 0.025). Of these 40, 22 pathways are common between the survivor and general population cohorts.

Mechanism	Pathway Name	Total Perturbation Score (tPert)	FDR-Adjusted pPert	Common or Distinct*
Inflammation/ Immune Response	Cytokine-cytokine receptor interaction	7.37	0.007	Common
	NF-kappa B signaling pathway	8.79	0.009	Common
	Chemokine signaling pathway	6.97	0.009	Common
	Phagosome	5.3	0.013	Common
	PPAR signaling pathway	7.24	0.007	Distinct
Neural Function & Development	Neuroactive ligand-receptor interaction	7.36	0.009	Common
	Axon guidance	5.32	0.017	Common
	Dorso-ventral axis formation	4.37	0.016	Distinct
Cellular Growth, Proliferation, Regulation	MAPK signaling pathway	6.81	0.007	Common
	ErbB signaling pathway	4.53	0.007	Common
	HIF-1 signaling pathway	6.4	0.009	Common
	Cell cycle	5.29	0.009	Common
	p53 signaling pathway	4.88	0.011	Common
	mTOR signaling pathway	5.27	0.015	Common
	PI3K-Akt signaling pathway	3.61	0.015	Common
	Wnt signaling pathway	4.62	0.015	Common
	Apoptosis	4.14	0.015	Common
	TGF-beta signaling pathway	4.32	0.017	Common
	Fanconi anemia pathway	12.6	0.007	Distinct
	Ribosome biogenesis in eukaryotes	11.2	0.007	Distinct
	Regulation of autophagy	5.04	0.011	Distinct
	Protein processing in endoplasmic reticulum	4.28	0.013	Distinct
	Hedgehog signaling pathway	4.33	0.016	Distinct
	Notch signaling pathway	3.54	0.016	Distinct
	VEGF signaling pathway	4.25	0.019	Distinct
	Hippo signaling pathway	4.43	0.020	Common
Cell Operations & Transport	Endocytosis	5.63	0.013	Common
	SNARE interactions in vesicular transport	4.52	0.011	Distinct
	Calcium signaling pathway	9.33	0.007	Distinct
	RNA degradation	7.68	0.007	Distinct
	RNA transport	7.14	0.007	Distinct
	mRNA surveillance pathway	5.46	0.007	Distinct
	Sulfur relay system	5.21	0.011	Distinct
Tissue-Specific & Structural Processes	Oocyte meiosis	5.5	0.009	Common
	Osteoclast differentiation	3.7	0.020	Common
	ECM-receptor interaction	4.39	0.020	Common
	Focal adhesion	3.79	0.020	Common
	Cardiac muscle contraction	6.03	0.015	Distinct
	Vascular smooth muscle contraction	3.69	0.015	Distinct
	Cell adhesion molecules (CAMs)	3.54	0.020	Distinct

Table 2: Results of PIA, showing significantly perturbed gene expression pathways in the cancer survivor group. Perturbed pathways unique to the survivor cohort are highlighted in red.
*As compared to perturbation in the general population.

Discussion

The results of the pathway analysis suggest that trait anxiety is mediated by cellular stress, neuroinflammation, and regulatory pathways. Unique to cancer survivors are nonsense-mediated decay pathways that could represent epigenetic changes caused as an effect of cancer and its treatment.

Conclusion

Trait anxiety severity is associated with inflammatory, regulatory, and neurodegeneration signaling pathways in survivors. Many, but not all, of these pathways are concordant with those perturbed in the general population. This suggests that common and distinct pathways may underlie trait anxiety in survivors.

Acknowledgements

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