Genetic associations of fatigue and other symptoms after breast cancer treatment

Results from a prospective cohort study

DR KATE WEBBER, DR BARBARA BENNETT,
PROF DAVID GOLDSTEIN, PROF ANDREW LLOYD

NSW CANCER SURVIVORS CENTRE, UNSW

Background

- Early identification of individuals at highest risk of physical and psychological issues following cancer treatment remains a key survivorship challenge
- Previously reported on natural history of common symptoms after cancer therapy in a cohort of >200 women with stage I/II breast cancer
  - Up to half had significant fatigue and/or mood disturbance at the end of adjuvant therapy
  - Self-limiting over <12 months for the majority
  - Persistent symptoms sig. associated with higher self-reported disability and health care utilisation

GOLDSTEIN D, BENNETT BK, WEBBER K, ET AL. CANCER-RELATED FATIGUE IN WOMEN WITH BREAST CANCER: OUTCOMES OF A 5-YEAR PROSPECTIVE COHORT STUDY. J CLIN ONCOL. 2012

FolCan findings

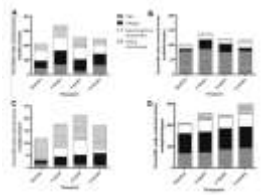
- Development of persistent fatigue or mood disturbance was not significantly associated with:
  - Demographic factors
  - Type of surgery or adjuvant therapy
  - Nodal stage
  - Hormone receptor status of tumour
- Physical and psychological symptoms may not be unique to cancer or its treatment, but stereotyped responses to an insult which are host determined

Endophenotypes

- Host response to insult (cancer, infection, trauma…) varies between individuals
  - Severity of illness
  - Dominant symptom domains of the illness response
- Likely that this variability has a genetic basis
- **Endophenotype:** symptom domain within a complex illness, with recognisable and stable characteristics, with a likely (or proven) genetic association
- Originally described in relation to mental illnesses (major depression, bipolar disorder, schizophrenia)
- More recently applied to physical illness, such as the acute sickness response after acute infection

Endophenotypes after acute infection

- **Dubbo Infection Outcome Study (DIOS):** prospective cohort recruited after acute viral illness
- Symptom domains of fatigue, pain, mood disturbance and neurocognitive difficulties derived
- Vary between but temporally stable within individuals
- Associations found with genes related to polymorphisms in pro- and anti-inflammatory cytokines
  - Fatigue and IFN-γ +874 T/A
  - Mood and IL-6 174 G/C and IL-10 592
  - Neurocognitive difficulties and IL-10 592



PIRAINO B, VOLLMER-CONNA U, LLOYD AR. GENETIC ASSOCIATIONS OF FATIGUE AND OTHER SYMPTOM DOMAINS OF THE ACUTE SICKNESS RESPONSE TO INFECTION. BRAIN BEHAV IMMUN. 2012 MAY;26(4):552–8.

FolCan endophenotypes study

- Aim to apply the principle of endophenotypes to the Folcan early breast cancer cohort
  - Prospective cohort of women with stage I/II breast cancer
  - Recruited after surgery but before adjuvant therapy
  - Followed with symptom questionnaires at baseline, end treatment, 3, 6, 9, 12 months
  - Optional participation in genetic substudy
- Questionnaires:
  - Somatic and Psychological Health Report (SPHERE)
  - Physical Symptoms Checklist (PSC)
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)
  - Blatt-Kupperman menopausal index (BMI)
- Symptom scales for pain, fatigue, mood disturbance and neurocognitive disturbance derived by PCA
  - assessed for reliability, correlation with disability scores and stability over time

Genetic analyses

- DNA extracted from peripheral blood mononuclear cells
- Functional single nucleotide polymorphisms (SNPs) sought for:
  - Cytokine and neuroregulatory genes (TNF-α, IFN-γ, IL-1B, IL-6, IL-10, NPY)
  - Purinogenic transporter gene, P2RX7 (exploratory analyses)
- Univariable and multivariable logistic regression associations sought between SNPs, clinical and demographic features and "high" or "low" levels of symptoms on each of the derived scales
- Association between SNPs and symptom trajectories explored with Kaplan-Meier time to recovery survival analyses

Results

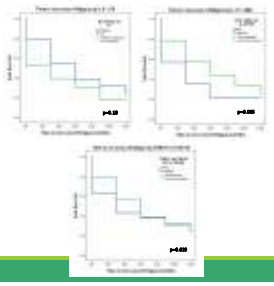
- Questionnaire data at end-treatment available for 210 women
- 111 unambiguously Caucasian with samples for genetic analysis
- Endophenotypes scales derived by PCA
  - mood disturbance scale separated into 2 components (depression and anxiety)
  - all scales reliable with Cronbach's alpha >0.87
- Higher scores on each of the scales were associated with greater self-reported disability at end-treatment (BDQ, days out of usual role)
  - fatigue (7.1 vs 2.5 days, p <0.001)
  - pain (7.3 vs 4.7 days, p=0.04)
  - depression (8.8 vs 4.2 days, p=0.001)
  - anxiety (8.5 vs 4.5 days, p=0.006)
  - neurocognitive (8.5 vs 4.5, p=0.006)

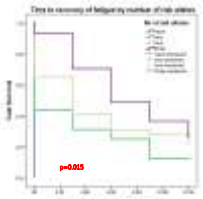
	Questionnaire only cohort (n= 89)		Genetic cohort (n=111)		
Characteristic	No	%	No	%	p
Age, years Mean (SD)	51.8 (10.6)		52.8 (10.1)		0.49
Completed ≥ 12 years education	66	67	61	58	0.26
Married or defacto	77	79	87	81	0.86
Employed or studying ≥ 20hrs/week	46	59	61	63	0.71
Pre-menopausal at baseline	47	50	53	52	0.95
Tumour characteristics					
Size, mm Mean (SD)	21.8 (12.9)		22.3 (14.6)		0.82
Positive lymph nodes	34	36	36	34	0.86
Oestrogen receptor positive	66	75	73	70	0.50
Surgical treatment					
Mastectomy	31	33	42	40	0.35
Axillary clearance	78	82	81	77	0.49
Adjuvant treatment					
Chemotherapy	61	64	75	72	0.30
Radiotherapy	71	75	75	72	0.80
Hormonal therapy	49	52	48	46	0.53

Regression models and genetic associations

Variables	p	Odds ratio (95% CI)	Model X^2 (p)
FATIGUE			
Working/studying >20 hours	**<0.001**	8.90 (2.61-30.3)	
IL-6 -174 GG/GC vs CC	**0.004**	7.88 (1.97-31.54)	29.726 (<0.001)
P2RX7 rs1718119 GG vs GA/AA	**0.034**	0.28 (0.09-0.91)	
IL-10 -1082 GG vs GA/AA	**0.010**	0.17 (0.05-0.66)	
PAIN			
P2RX7 rs1653624 TT vs TA	0.110	6.01 (0.67-54.25)	
P2RX7 rs1718119 GG vs GA/AA	**0.040**	0.38 (0.15-0.96)	14.672 (0.002)
Working/studying >20 hours	**0.025**	2.89 (1.14-7.32)	
DEPRESSION			
Age	**0.015**	0.93 (0.88-0.99)	
IL-10 -1082 GG/GA vs AA	**0.002**	0.21 (0.07-0.57)	16.467 (<0.001)
P2RX7 rs208294 TT vs TC/CC	**0.014**	4.21 (1.33-13.25)	
ANXIETY			
Age	**0.028**	0.95 (0.90-0.99)	
P2RX7 rs208294 AA vs AG/GG	**0.009**	4.36 (1.44-13.14)	24.184 (<0.001)
IL-10 -1082 GG/GA vs AA	**<0.001**	0.16 (0.06-0.43)	
NEUROCOGNITIVE DIFFICULTIES			
Age	0.063	0.96 (0.91-1.00)	14.649 (0.002)
TNF -308 GG vs GA/AA	**0.030**	2.92 (1.11-7.68)	

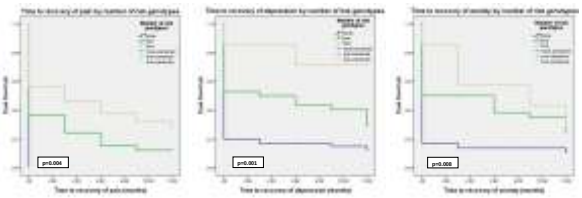
Polymorphisms and symptom time course





Number of risk alleles	Median time to recovery (months, 95% CI)
0	0
1	0
2	3 (1.2 – 4.8)
3	6 (4.4 – 7.6)

Trajectories for other symptoms



Discussion

- Findings suggest that susceptibility to adverse symptoms after cancer therapy have a genetic basis
- Support the work of others that cytokine gene SNPs, in particular IL-6, IL-10 and TNF-α are associated with the risk of fatigue, mood disturbance and neurocognitive difficulties after breast cancer
- Report for the first time associations between P2RX7 transporter gene SNPs and some of these symptoms in a cancer cohort
- Some of these findings have also been reported outside of cancer:
  - IL-10 -1082 and depression in end-stage renal disease and stroke
  - TNF-α -308 and attentional processing in healthy individuals
  - P2RX7 rs208294 and anxiety, major depression and trait neuroticism
- Limitations
  - sample size
  - choice of self-report questionnaires – sensitivity of instruments
  - complex polygenic phenomena

Conclusions

- Mood disturbance, pain, fatigue and neurocognitive dysfunction after cancer therapy have a genetic basis
- May represent inherent susceptibility to these symptoms rather than a response unique to cancer or its treatment
- Personalised cancer therapy
  - tumour genotype - optimum therapy
  - somatic genotype - likelihood of toxicity