About George Engel and Mechanisms of Stress Effects on Cancer Metastasis

September 19, 2013

Anil K. Sood, M.D., Professor
Vice Chair, Translational Research
Departments of Gynecologic Oncology and Cancer Biology
Co-Director, Center for RNAi and Non-Coding RNA
Director, Blanton-Davis Ovarian Cancer Research Program
Evidence of Social Origins of Adverse Health Outcomes

Anil K. Sood, M.D.

• About George Engel and mechanisms of stress effects on cancer metastasis

Lisa Christian, Ph.D.

• Effects of stress and depression on immune measures in pregnancy

William M. Callaghan, M.D., M.P.H.

• Geographic variation of reproductive health indicators and outcomes: Place matters
George L. Engel (1913 – 1999)

The Biopsychosocial Model

“........biological factors alone cannot account for all changes in physical health and behavioral aspects must also be considered..........”

Engel GL. Science, 1977
Negative Effects of Chronic Stress

- Psychological – depression, anxiety
- Heart disease – vessel constriction, rhythm disturbance, blood clots, ↑cholesterol, ↑blood pressure
- Stroke
- Susceptibility to infections
- **Cancer progression**
- Gastrointestinal: Irritable Bowel Syndrome, peptic ulcers, inflammatory bowel disease; Eating problems (weight gain, weight loss, anorexia, bulimia)
- Diabetes
- Pain
- Sleep disturbances
Stress Effects on Cancer Biology: Conceptual Framework

Physiologic Stress Response Systems
- SNS
- HPA axis
- Other stress hormones
- Immune system
- Metabolic systems

Tumor Microenvironment
- Proliferation & metastasis
- Adhesion
- Migration & invasion
- Cell survival
- Angiogenesis

Disease Course & Treatment Response
- Tumor growth
- Tumor progression
- Treatment resistance

Individual Macroenvironment
- Depression
- Social isolation
- Social status
- Social support
- Personality
- Early life events
- Coping
Biobehavioral Risk Factors and Cancer Progression

1. In 330 studies, stress-related psychosocial factors were associated with poorer cancer survival ($P<0.001$)

2. Largest survival effects documented for:
   - Hepatobiliary cancer 1.88 (1.07-3.30)
   - Head and neck cancer 1.58 (1.22-2.03)
   - Lymphoid or hematopoietic cancer 1.32 (1.11-1.56)
   - Lung cancer 1.17 (1.03-1.34)
   - Breast cancer 1.13 (1.05-1.21)

3. In 53 studies, stress-related psychosocial factors were associated with higher cancer mortality ($P<0.001$)

Chida et al. (2008) Nature Clinical Practice Oncology
# Neuroendocrine Influences on Tumor Viruses

<table>
<thead>
<tr>
<th>Human tumor virus</th>
<th>Malignancy</th>
<th>Sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV 16 and 33</td>
<td>Cervix and head/neck</td>
<td>HPA</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Hepatocellular</td>
<td>HPA</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>Hepatocellular</td>
<td>HPA</td>
</tr>
<tr>
<td>Epstein-Barr virus</td>
<td>Lymphoma and nasopharyngeal</td>
<td>HPA</td>
</tr>
<tr>
<td>HTLV 1 and 2</td>
<td>Adult T-cell leukemia/lymphoma</td>
<td>ANS</td>
</tr>
<tr>
<td>Kaposi sarcoma-associated Herpesvirus</td>
<td>Kaposi sarcoma &amp; primary effusion</td>
<td>ANS</td>
</tr>
</tbody>
</table>

Antoni et al., *Nature Reviews Cancer*, 2006
Are biobehavioral factors associated with cancer outcome?

• Yes - consistent associations documented for cancer survival and mortality
• Equivocal findings for cancer incidence/initiation
Effects of Chronic Stress on Tumor Microenvironment
Exposure to chronic stress promotes tumor growth and angiogenesis

- Use of mouse host-human tumor hybrid model
- First experimental evidence that behavioral stressors can enhance pathogenesis of ovarian carcinoma \textit{in vivo}
- Neuroendocrine stress response affects the growth and activity of malignant tissue through hormone receptors expressed by tumor cells

\textit{Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma}

Thaker et al. (2006)
Exposure to chronic stress: Ovarian cancer growth *in vivo*

Thaker et al. (2006) *Nature Medicine*
Vascular Endothelial Growth Factor and Social Support in Patients with Ovarian Carcinoma

Susan K. Lutgendorf, Ph.D.1
Erica L. Johnsen, M.A.1
Brian Cooper, M.D.2
Barrie Anderson, M.D.2
Joel I. Sorosky, M.D.2
Richard E. Buller, M.D., Ph.D.2
Anil K. Sood, M.D.2

1 Department of Psychology, University of Iowa, Iowa City, Iowa.
2 Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Iowa, Iowa City, Iowa.

BACKGROUND. The modulation of immunologic activities relevant to cancer by behavioral factors, such as stress, depression, and social support, is well documented. However, associations of behavioral factors with cytokines involved in tumor angiogenesis have not been studied. Vascular endothelial growth factor (VEGF) is a key cytokine that is capable of stimulating tumor angiogenesis, and it has been associated with poorer survival in patients with ovarian carcinoma. VEGF is modulated by a variety of behaviorally sensitive factors, including sympathetic activation. This study examined relationships of social support and depressive symptoms with VEGF levels in preoperative patients with ovarian carcinoma.

METHODS. Twenty-four women with ovarian carcinoma and 5 women with benign pelvic masses were recruited at the presurgical clinic visit, received psychosocial surveys, including the Functional Assessment of Cancer Therapy (Quality of Life) survey and the Profile of Mood States, and a blood draw. Serum VEGF levels were assessed by enzyme-linked immunosorbent assay. Analyses controlled for disease stage.

RESULTS. Women with ovarian carcinoma who reported higher levels of social well being had lower levels of VEGF ($P = 0.005$). Greater support from friends and neighbors ($P = 0.005$) and less distance from friends ($P = 0.04$) were facets of social
Experimental stress effects on angiogenesis

Thaker et al. (2006) *Nature Medicine*
Beta-adrenergic signaling in cancer

Cole and Sood. *Clin Cancer Res*; 18(5); 1201–6
The third catecholamine: dopamine

Legend:
- Control
- Restrained

Moreno-Smith, et al., Clin Cancer Res, 2011
Effects of dopamine on stress-induced tumor growth

Moreno-Smith, et al., Clin Cancer Res, 2011
Summary-2:
Stress effects on ovarian carcinoma growth *in vivo*

- Enhanced tumor growth and progression
- Two molecular mechanisms identified:
  1. Stress regulation:
     - Catecholamine signaling *via* beta-adrenergic receptors
     - Depletion of dopamine
  2. Tumor biology:
     Up-regulated angiogenesis

Implication: β-blockade or dopamine agonists might help slow tumor progression in human ovarian cancer.
Clinical Implications
Impact of Social Support in Ovarian Cancer Patients

Lutgendorf, et al., J Clin Oncol, 2012

$P < 0.018$
Primary ovarian epithelial carcinomas

- **Group 1:** high depressive sx (CESD) and low social support
- **Group 2:** low depression (CESD) and high social support
- Matched on Grade, Stage, and histological subtype

Global gene expression profiling

Bioinformatics:

- Identify differentially expressed genes (> 2-fold)
- Define common features of regulated genes:
  - Function: GOstat / Gene Ontology clustering
  - Regulation: TELiS / Transcription Factor activity

*Lutgendorf et al., Brain, Behavior, and Immunity, 2009*
Depression and Gene Expression in Ovarian Cancer

220 up-regulated
46 down-regulated

High Depression & Low Social Support
Low Depression & High Social Support
Signaling Pathways

- **CREB**
  - p = .007
- **NF-κB**
  - p = .008
- **STAT3**
  - p = .013
- **ELK1**
  - p = .045

**Significance:**
- NE / βAR signaling
- Inflammation
- Metastatic capacity
- MAPK activity: proliferation

*Lutgendorf, et al, BBI, 2009*
Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study

Dean Ornish, Jue Lin, Jane M Chan, Elissa Epel, Colleen Kemp, Garth Weidner, Ruth Marlin, Steven J Friend, Mark Jesus M Magbanua, Jennifer Daubmann, Eve Estay, Nancy K Hills, Nita Chanani-Wu, Peter R Carroll, Elizabeth H Blackburn

Summary
Background Telomere shortness in human beings is a prognostic marker of ageing, disease, and premature morbidity. We previously found an association between 3 months of comprehensive lifestyle changes and increased telomerase activity in human immune-system cells. We followed up participants to investigate long-term effects.

Methods This follow-up study compared ten men and 25 external controls who had biopsy-proven low-risk prostate cancer and had chosen to undergo active surveillance. Eligible participants were enrolled between 2003 and 2007 from previous studies and selected according to the same criteria. Men in the intervention group followed a programme of comprehensive lifestyle changes (diet, activity, stress management, and social support), and the men in the control group underwent active surveillance alone. We took blood samples at 5 years and compared relative telomere length and telomerase enzymatic activity per viable cell with those at baseline, and assessed their relation to the degree of lifestyle changes.

Findings Relative telomere length increased from baseline by a median of 0.06 telomere to single-copy gene ratio (T/S) units (IQR -0.05 to 0.11) in the lifestyle intervention group, but decreased in the control group (-0.03 T/S units, -0.05 to 0.03, difference p=0.03). When data from the two groups were combined, adherence to lifestyle changes was significantly associated with relative telomere length after adjustment for age and the length of follow-up (for each percentage point increase in lifestyle adherence score, T/S units increased by 0.07, 95% CI 0.02-0.12, p=0.005). At 5 years, telomerase activity had decreased from baseline by 0.25 (-2.25 to 2.23) units in the lifestyle intervention group, and by 1.08 (-3.25 to 1.86) units in the control group (p=0.64), and was not associated with adherence to lifestyle changes (relative risk 0.93, 95% CI 0.72-1.2.0, p=0.57).

Interpretation Our comprehensive lifestyle intervention was associated with increases in relative telomere length after 5 years of follow-up, compared with controls, in this small pilot study. Larger randomised controlled trials are warranted to confirm this finding.
Beta-Blocker Use Is Associated With Improved Relapse-Free Survival in Patients With Triple-Negative Breast Cancer

Amal Mehlmen-Bertrand, Mariana Chavez-MacGregor, Xiudong Lei, Erika N. Brown, Richard T. Lee, Fusuki Mertis-Bernsain, Anil K. Sood, Gabriel N. Hortobagyi, Ana M. Gonzalez-Angulo


ABSTRACT

Purpose
To examine the association between beta-blocker (BB) intake, pathologic complete response (PCR) rates, and survival outcomes in patients with breast cancer treated with neoadjuvant chemotherapy.

Patients and Methods
We retrospectively reviewed 1,413 patients with breast cancer who received neoadjuvant chemotherapy between 1995 and 2007. Patients taking BBs at the start of neoadjuvant therapy were compared with patients with no BB intake. Rates of pCR between the groups were compared using a χ² test. Cox proportional hazards models were fitted to determine the association between BB intake, relapse-free survival (RFS), and overall survival (OS).

Results
Patients who used BBs (n = 102) were compared with patients (n = 1,311) who did not. Patients receiving BBs tended to be older and obese (P < .001). The proportion of pCR was not significantly different between the groups (P = .48). After adjustment for age, race, stage, grade, receptor status, lymphovascular invasion, body mass index, diabetes, hypertension, and angiotensin-converting enzyme inhibitor use, BB intake was associated with a significantly better RFS hazard ratio (HR) 0.30 (95% CI 0.31 to 0.88) but not OS (P = .09). Among patients with triple-negative breast cancer (TNBC; n = 377), BB intake was associated with improved RFS (HR, 0.30; 95% CI, 0.10 to 0.87; P = .027) but not OS (HR, 0.35; 95% CI, 0.12 to 1.00; P = .05).

Conclusion
In this study, BB intake was associated with improved RFS in all patients with breast cancer and in patients with TNBC. Additional studies evaluating the potential benefits of beta-adrenergic blockade on breast cancer recurrence with a focus on TNBC are warranted.

J Clin Oncol 29. © 2011 by American Society of Clinical Oncology
Beta-blocker usage and outcome of patients with ovarian cancer

- Multicenter review of 1,425 patients with epithelial ovarian cancer
- Median age 61 years (range: 31-93)

\[ P<0.001 \]

Watkins, et al., SGO, 2013
Average of 17% reduction across all cancer types
Summary-3:
Effects of stress on tumor microenvironment

Antoni et al., *Nature Reviews Cancer*, 2006
Acknowledgements

Collaborators
Susan Lutgendorf
Steve Cole
Yu Kang
Tao Liu
Michael Deavers
Premal Thaker
Koen De Geest
Vikas Kundra
Jim Bankson
Gabriel Lopez-Berestein

Support
NCI (CA 109298, CA 110793, SPORE)
DOD, OCRF

Lab Team
Guillermo Armaiz-Pena
Archana Nagaraja
Kshipra Gharpure
Chunhua Lu
Myrthala Moreno-Smith
Nicholas Jennings
Bhavin Shah
L. Mangala
Heather Dalton
Behrouz Zand
Chad Pecot
Rajesha Rupaimoole
Yu Kang
Tao Liu
Wei Hu
Sherry Wu