

Social Factors Influencing Cancer Risk and Progression



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Social Relationships and Health

JAMES S. HOUSE, KARL R. LANDIS, DEBRA UMBERSON

- “Social relationships, or the relative lack thereof, constitute a major risk factor for health-rivaling the effect of well established health risk factors such as cigarette smoking, blood pressure, blood lipids, obesity and physical activity.”

- *House, Landis, and Umberson: Science, 1988*



Social Relationships and Mortality Risk: A Meta-analytic Review

Julianne Holt-Lunstad^{1,3*}, Timothy B. Smith^{2,3}, J. Bradley Layton³

July 2010

- 148 Studies (308,849 participants)
- Average effect size OR=1.50 (95% CI 1.42 to 1.59) (50% increased likelihood of survival for participants with stronger social relationships)
- Consistent across age, sex, initial health status, cause of death, and follow-up period
- Risk differs according to type of measurement
- Associations strongest for social integration OR=1.91 (95% CI 1.63 to 2.23)
- Weakest for binary measurements such as residential status OR=1.19 (95% CI .99 to 1.44)

Stress Buffering and Main Effects Models of Social Support (*Cohen & Wills, 1985*)

Buffering:

- Relationships buffer deleterious influence of stressors on health
- perception of event as less stressful
- may improve ability to cope
- may improve adherence to medical regimens
- may improve positive health behaviors



Direct Effects of Social Support

- Social relationships have benefits at all times, not only during non-stressful periods
- May encourage or model healthy behaviors
- Conformity to social norms relevant to health and self care
- Meaningful roles that provide self esteem and purpose



How are social roles defined?

- Structural:
 - Degree of integration in social network
 - eg. married, number and frequency of contacts with children, close relatives, close friends
- Functional:
 - Social interactions
 - Perceptions of support availability

Social Support/Isolation and Cancer Progression

- Pinqart & Duberstein (2009)
 - High levels of perceived social support associated with decreases in relative risk for cancer mortality
- Weihs et al (2008)
 - Breast cancer patients with close relationships (confiding marriage and dependable non-household supports) had better survival.
- Sprehn et al. (2009)
 - Patients separated at time of cancer diagnosis had poorest five-and ten-year relative survival rates relative to rates observed in other marital status categories
- Kroenke et al (2006)
 - Two-fold increase in mortality risk for socially isolated breast cancer patients (Stages 1-4) vs. women with large social networks.
- Villingshoj et al (2006)
 - Loss of a partner prior to surgery associated with increased mortality risk in colorectal cancer patients

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ORIGINAL REPORT

Social Networks, Social Support, and Survival After Breast Cancer Diagnosis

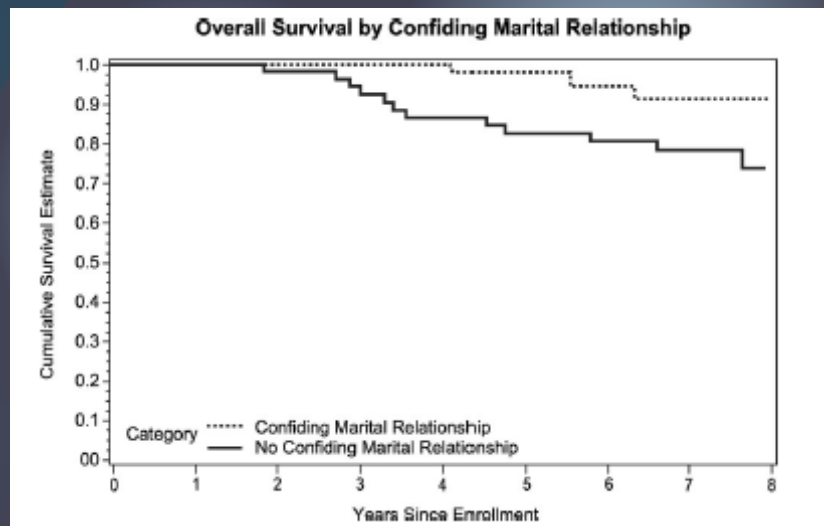
Candyce H. Kroenke, Laura D. Kubzansky, Eva S. Schernhammer, Michelle D. Holmes, and Ichiro Kawachi

- Participants: 2835 women from Nurses' Health Study diagnosed with stages I to IV breast cancer between 1992 and 2002
- Social networks: Assessed in 1992 (prior to dx), 1996, and 2000 with Berkman-Syme Social Networks Index
- Social emotional support: presence and availability of a confidant: 1992 and 2000

Kroenke et al. 2006

- Socially isolated women (before diagnosis) had a 66% increased risk of all-cause mortality (HR=1.66; 95% CI, 1.04 to 2.65) and a two-fold increased risk of breast cancer mortality (HR=2.14; 95% CI 1.11 to 4.12) compared to socially integrated women.
- Lack of close relatives, friends, or living children related to elevated risk of both all cause mortality and breast cancer mortality (HR 's 2.65-5.62)
- Participation in religious or community activities, being married, and having confidant not related to outcomes.
- Mechanisms: lack of access to care, lack of beneficial caregiving from friends, relatives, and children.

Survival by Confiding Marital Relationship in Breast Cancer Patients (Weihs et al, 2008)

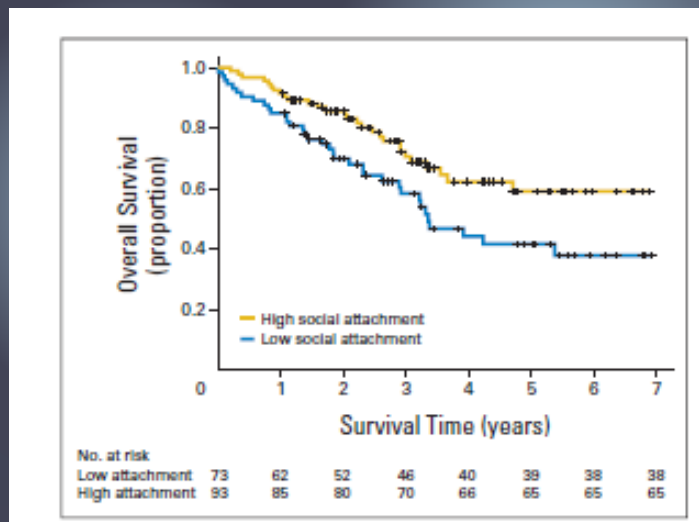


Social Influences on Clinical Outcomes of Patients With Ovarian Cancer

Susan K. Lutgensdorf, Koen De Geest, David Bender, Amina Ahmed, Michael J. Goodheart, Laila Dahmsvath, M. Bridget Zimmerman, Frank J. Persico, Joseph A. Lucci III, Parvin Ganji-Azar, Premal H. Thaker, Luis Mendez, David M. Lubareff, George M. Slavich, Steven W. Cole, and Arif K. Sood

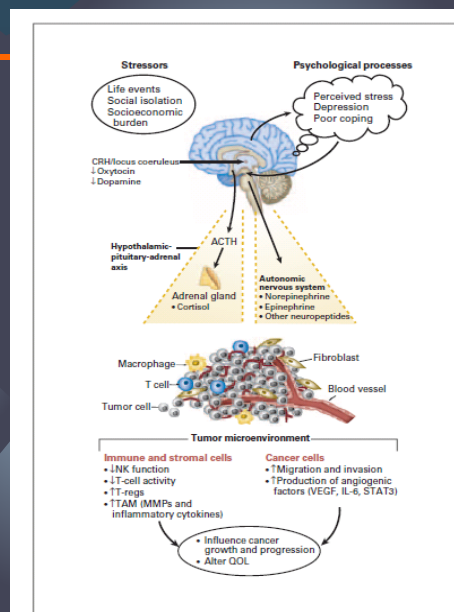
- 168 patients high and low in social support
- Low social support: Median survival was 3.35 years (95% CI 2.56 to 4.15 years)
- High Social Support: 59% of patients still alive at end of study, last death was at 4.7 years
- Attachment vs. Instrumental Social Support

Kaplan-Meier Table for High vs. Low Social Support and Survival in EOC



What are mechanisms underlying relationships between the social environment and cancer progression?

Conceptual Model: Effects of Stress on Tumor Microenvironment

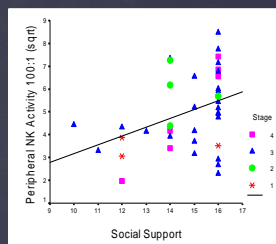


Social Support and Immunity in Early Stage Breast Cancer

Levy et al, 1987, 1990, 1991

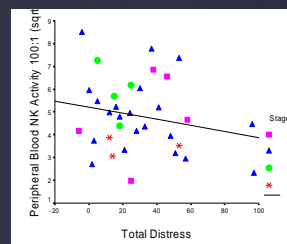
- Greater social support at surgery predicts higher NK cell activity concurrently and 15 months later
- Greater NK cell activity at 15 months related to longer disease free interval over 5-8 years.
- Distress and low social support predict faster disease progression over 5-8 years.

Social Support, Distress and NKCC (100:1) in PBMC and Tumor in Ovarian Cancer Patients

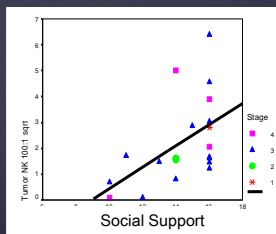


$\beta = .38, p = .024$

PBMC

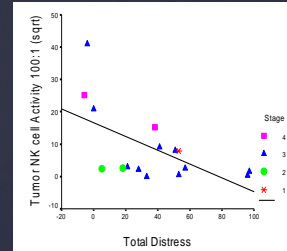


$\beta = -.21, p = 0.25$



$\beta = .47, p = .048$

TIL



$\beta = -.58, p = 0.02$

SOCIAL SUPPORT

DISTRESS

Covariate: stage

Lutgendorf et al, J Clinical Oncology, 2005

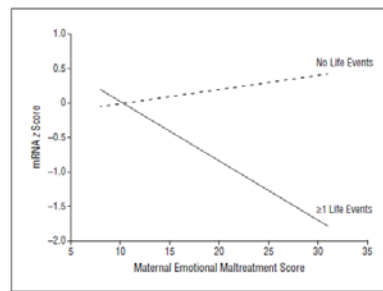
Basal Cell Carcinoma

Stressful Life Events and the Tumor Environment

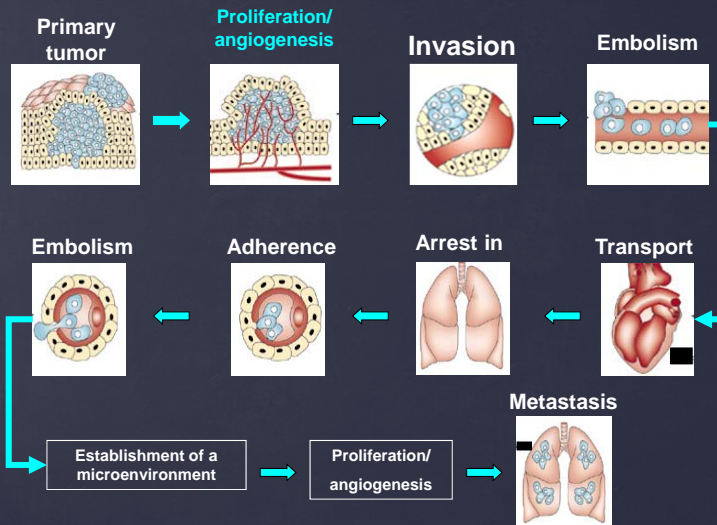
Christopher P. Fagundes, PhD; Ronald Glaser, PhD; Sheri L. Johnson, PhD; Rebecca R. Andridge, PhD; Eric V. Yang, PhD; Michael P. Di Gregorio, MS; Min Chen, MS; David R. Lambert, MD; Scott D. Jewell, MD; Mark A. Bechtel, MD; Dean W. Hearne, MD; Joel B. Herron, MD; Janice K. Kiecolt-Glaser, PhD

- In BCC patients experiencing > 1 current life stressor, early social adversity associated with poorer cellular immune response within the tumor (CD25, CD3e, CD68, ICAM-1) in later life.

(Am J Psychiatry, 2012)

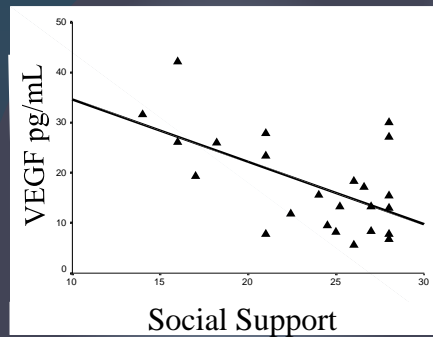


Steps in Formation of Metastases



Fidler, Nat Rev Cancer, 2003

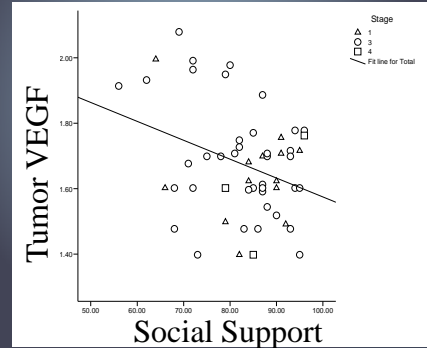
Social Support and VEGF in Ovarian Cancer Patients



$$\beta = -.57, p = .005$$

(Lutgendorf et al, *Cancer*, 2002)

Covariate: cancer stage.



$$\beta = -.31, p = .036$$

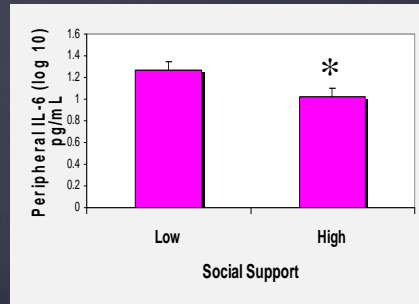
(Lutgendorf et al, *Clinical Cancer Research*, 2008)

Loneliness, Distress Linked to Higher VEGF in Colon Cancer

- Loneliness related to higher VEGF at the time of surgery (*Nausheem et al, 2010*)
- Depression and poor QOL related to higher VEGF at surgery and at 6 months (*Sharma et. al, 2007*).
- Both control for biomedical variables

Social Support and IL-6 in Advanced Ovarian Cancer Patients

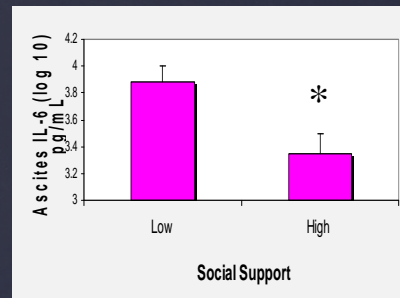
Peripheral IL-6



$p=0.028$

Covariates: stage; age

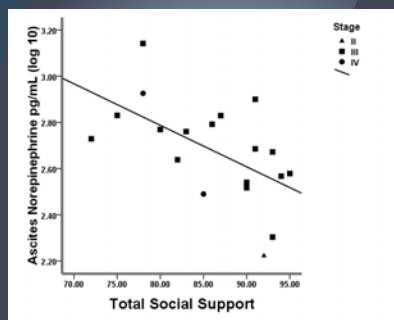
Ascites IL-6



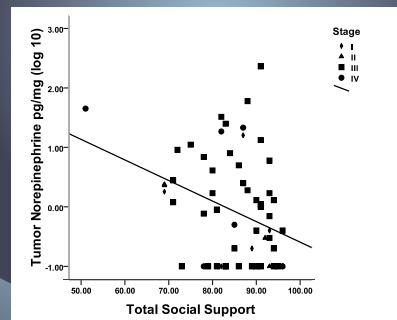
$p=0.04$

(Costanzo et al, *Cancer*, 2005)

Social Support and NE in Ovarian Cancer Patients



Ascites

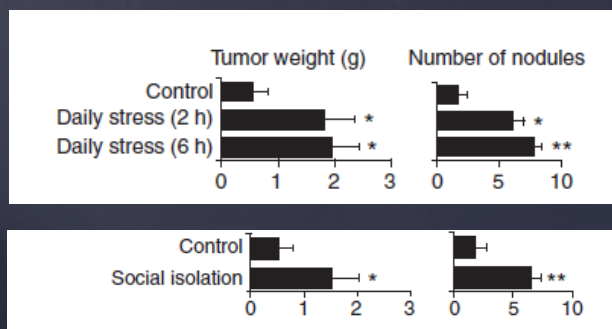


Tumor

Lutgendorf et al, *Brain Behavior and Immunity*, 2010

Chronic stress promotes tumor growth and angiogenesis in a mouse model of ovarian carcinoma

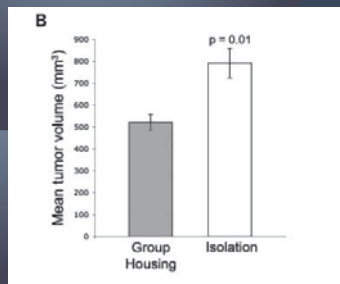
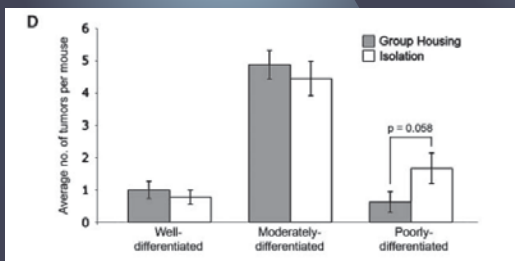
Premal H Thaker^{1,10}, Liz Y Han^{1,10}, Aparna A Kamat^{1,10}, Jesusa M Arevalo², Rie Takahashi², Chunhua Lu¹, Nicholas B Jennings¹, Guillermo Armaiz-Pena¹, James A Bankson³, Murali Ravoori⁴, William M Merritt¹, Yvonne G Lin¹, Lingegowda S Mangala¹, Tae Jin Kim¹, Robert L Coleman¹, Charles N Landen¹, Yang Li¹, Edward Felix², Angela M Sanguino⁶, Robert A Newman², Mary Lloyd⁷, David M Gershenson¹, Vikas Kundra^{4,8}, Gabriel Lopez-Berestein⁶, Susan K Lutgendorf⁹, Steven W Cole² & Anil K Sood^{1,7}



A Model of Gene-Environment Interaction Reveals Altered Mammary Gland Gene Expression and Increased Tumor Growth following Social Isolation

J. Bradley Williams,¹ Diana Pang,¹ Bertha Delgado,^{2,3} Masha Kocherginsky,⁴ Maria Tretiakova,² Thomas Krausz,² Deng Pan,¹ Jane He,¹ Martha K. McClintock³ and Suzanne D. Conzen^{1,3,5}

- Chronic social isolation in mice associated with upregulated gene expression in 2 metabolic pathways linked to increased growth of breast cancer.



Social Support/Loneliness and Leukocyte Gene Expression

- Loneliness: over expression of genes involved in immune activation and inflammatory expression; under expression of genes related to glucocorticoid functioning (Cacioppo et al., 2007)

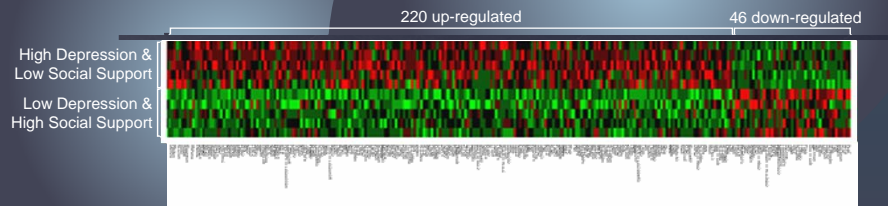


Psychosocial Risk Factors and Regulation of Tumor Gene Expression

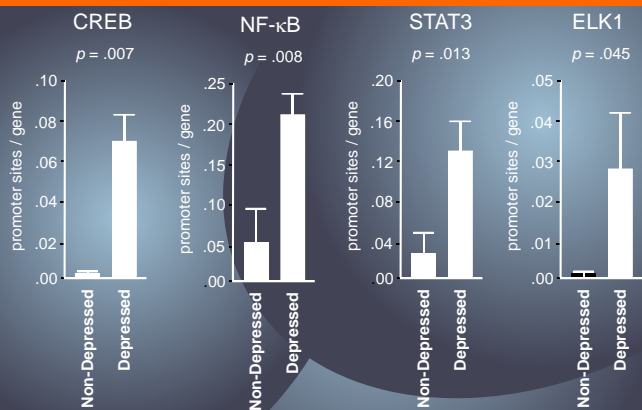
- 10 primary ovarian epithelial carcinomas
 - 5 pt. with high depressive sx (CESD) and low social support
 - 5 pt. with low depression (CESD) and high social support
 - matched on Grade, Stage, and histological subtype
- Global gene expression profiling
 - Affymetrix U133A high-density oligonucleotide arrays
 - simultaneous hybridization in UCLA / Jonsson Cancer Center DNA Microarray Core
 - low-level expression analysis by Robust Multi-array Averaging (RMA)
- Bioinformatics 1: Identify differentially expressed genes
 - Average difference > 2-fold
- Bioinformatics 2: Define common features of regulated genes
 - Function: Gostat / Gene Ontology clustering
 - Regulation: TELiS / Transcription Factor activity
- Differential gene expression confirmed by quantitative RT-PCR

Lutgendorf, ...Cole, Brain, Behavior, and Immunity, 2009

Social Support/ Depression and Gene Expression in Ovarian Cancer



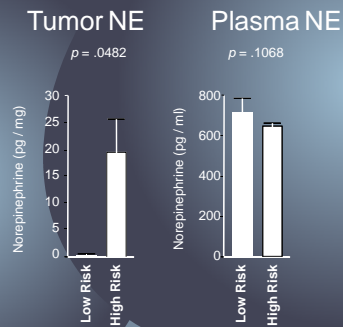
Signaling Pathways



Significance: NE / β AR signaling Inflammation Metastatic capacity MAPK activity: proliferation

Lutgendorf, ...Cole, Brain, Behavior, and Immunity, 2009

Plasma and Tumor Norepinephrine in High and Low Risk Patients

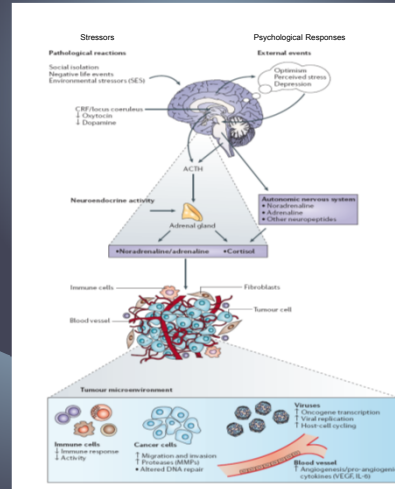


Lutgendorf, ... Cole, Brain Behavior and Immunity, 2009

- Distinctive gene expression fingerprint in primary ovarian tumors from pts with high depressive sx and low social support
- More than 200 genes over-expressed:
 - Growth-regulating transcription factors
 - Extracellular matrix
 - Proteases
 - Chemokines, receptors, and adhesion molecules
- Potential transcriptional mediators:
 - CREB
 - NF-kB
 - Jak/Stat
 - MAPK/ELK1

Summary

- Social isolation associated with expression of molecules supporting tumor growth, angiogenesis, and invasion in the tumor microenvironment in a variety of tumor models.
- Clinical implications



Emerging Questions

- Are there social/emotional developmental periods that set up individuals for vulnerability to cancer incidence/progression later in life?
- Stress inhibiting factors (resilience, social support); how much is enough
- Are these pathways different for males vs. females?
- Interactions with diet, toxins, metabolic factors?



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