

A wide range of psychosocial factors have been inconsistently associated with the course of established cancers due to the heterogeneity in:

- samples of patients studied (e.g., mixed cancer types and stages),
- psychosocial variables assessed
- psychosocial interventions used
- study designs, control variables and analytic procedures employed

Psychosocial variables may relate more reliably to health outcomes in cancers that are:

- earlier stages
- controlled to some degree by immunologic or endocrine processes known to be associated with psychosocial factors.

Cancer Type

Cancers whose progression appears to be associated with psychosocial factors on the one hand and immune or endocrine system components on the other include:

- malignant melanoma
- breast cancer
- prostate cancer
- virally-related cancers
 - cervical cancer
 - Burkitt's lymphoma
 - Kaposi's Sarcoma
 - hepatocellular carcinomas.

Cancer Initiation/Promotion (Eg., Cervical Intraepithelial Neoplasia)

- Life stress
- Pessimism/Hopelessness
- Passive coping
- Social Isolation

Cancer Progression/Relapse (e.g., Breast Cancer)

- Elevated life stressors and relapse or shortened survival time after treatment
- Elevated stress levels after adjuvant therapy
- Poor expression of anger
- Stoicism
- Repressiveness/non-expression of emotion
- Lack of social support

Some key questions that are now emerging in the field of psychoncology include:

- What are the consistent psychosocial predictors of cancer disease progression?
- What are their likely mediators and effects sizes?
- How can these associations be used to inform psychosocial interventions?

The Role of the Immune System in Cancer

- *Initiation and promotion* of neoplastic disease process in a person who is at risk for cancer
- *Recurrence (and metastases)* of cancer in an individual who has been provided with curative and adjuvant treatments.
- Certain aspects of the immune system are particularly well-equipped to respond to the *initiation or recurrence* of tumor growth.
- Several tumor-relevant immunologic measures have not been well studied by psycho-oncology investigators.

Immune Repertoire and Cancer *Initiation and Promotion*

- Antibodies and complement
- Phagocytes
- Cytotoxic T lymphocytes
- Antibody dependent cellular cytotoxicity (ADCC) and NK cell cytotoxicity (NKCC)
- Cytokine-activated macrophages and NK cells
- CD4+T-lymphocyte-mediated macrophage tumoricidal activity initiated by γ -IFN.

Tumor Relevant Immune Functions

- ADCC involves binding of tumor-specific antibodies to the surface of tumor cells, interacting with other cells with Fc receptors (e.g., NK cells)
- ADCC has been shown to decrease with progression of some cancers (Satam, Suraiya & Nadkarni, 1986).
- NKCC does not require binding to an antigen-specific receptor.
- NK cells may represent a first line of defense against the growth of transformed cells at both *primary* and *metastatic* sites
- T-cell mediated immunity may also play a role in tumor recognition and cytolytic activity.

Immunologic Repertoire and Cancer *Progression and Recurrence*

- NK cells and CTLs believed to play an important role in the host response against shed tumor cells, thus preventing metastases
- In patients with solid tumors, greater NKCC predicted longer survival time without metastases over a 13-year period
- Lower NKCC predicted development of local recurrence of colorectal cancer and distant metastases in patients with head and neck tumors
- As breast cancer progresses from Stage II to IV, NKCC, T-lymphocyte number and responsivity to mitogens becomes significantly reduced
- Patients with lower T lymphocyte counts and responsivity to mitogen prior to surgery had a higher risk for recurrent disease

Role of the Immune System in Cancer

Psycho-Oncology models of cancer disease recurrence rely on:

- Characterizing cell subpopulation phenotypes and receptor expression underlying
 - dendritic cell and macrophage-mediated antigen processing and presentation
 - NKCC/LAK cell cytotoxic activity and lymphoproliferative responses
- Considering the roles of IL-2 and IFN- γ and other cytokines involved in these processes

Psychosocial-Endocrine-Immune Mechanisms In Cancer Patients

- HPG hormones such as estrogens, progesterone and testosterone effects on the immune system, or directly on tumors themselves
 - estradiol and testosterone administration cause NKCC reductions
 - estrogen increases during the menstrual cycle and pregnancy are associated with NKCC declines.
 - progesterone suppresses NKCC and may additively suppress NKCC when combined with estrogens which could be due to a down regulation of gamma-interferon (γ -IFN) production.

Endocrine Factors and Cancer Promotion

- May play a larger role than the immune system in the initiation and promotion of breast and prostate cancers.
- Chief reproductive or hypothalamic-pituitary gonadal (HPG)-related hormones that have been associated with human cancers are testosterone (for PRCA and BRCA) and estrogens (BRCA)
- Good evidence from animal and human studies that testosterone, estrogen, progesterone and prolactin may contribute to the development of breast cancer
- Anti-estrogen agents such as Tamoxifen have been shown to be efficacious in reducing the risk of invasive breast cancer by 49% and non-invasive breast cancer by 50%
- It may be that a *normalization* of HPG levels is a key to maintaining health in patients who have developed or are at risk for breast cancer.

Summary: Relevance of Mind Body Research in Cancer

- Not all cancers are ideal candidates for examining psychosocial factors in relation to initiation and promotion.
- Some cancers may be associated with genetic, environmental, or nutritional factors that can initiate a carcinogenic process that escapes the surveillance of the immune system
- Some are determined by HPG regulation, independent of immune system
- For virally-initiated neoplastic changes or *recurrence* of some cancers the immune system may affect the course of disease.

Psychosocial-Immune Associations In Cancer Research

Stress and other psychosocial variables have been associated with immune measures possibly relevant to cancer or cancer-risk populations:

- T-lymphocytes that kill cancerous cells (CTLs or CD8+ T cells)
- Lymphocyte proliferative responses to challenge (LPR to anti-CD3 or PHA)
- NK cells and NKCC

Still a Disconnect Between:

- Studies relating stress and psychosocial factors to immune status
- Studies relating these psychosocial factors to disease relapse and survival in cancer patients

Burning Question

- **P-N-I-Disease:** E.g., Do the ways people respond to stressors (coping strategies, use of social support) relate to changes in NKCC, which in turn predict disease-free interval and survival time?

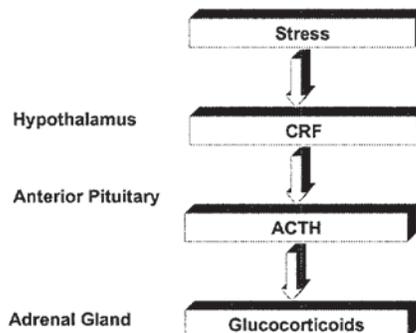
Psychosocial-Endocrine-Immune Mechanisms In Cancer Patients

- One of the most commonly cited explanations for stress-immune associations concerns the endocrine changes that are believed to occur during and after one's appraisals of and coping responses to stressor events
- An individual's perception of the availability of a coping response in a stressful situation has been evidenced to trigger a series of physiological events which lead to specific neurological, endocrine, and immunologic responses.

Psychosocial-Endocrine-Immune Mechanisms In Cancer Patients

- Hypothalamic-pituitary-adrenocortical system (HPAC)
 - cortisol has been shown to have suppressive effects on a number of components of the immune system that may be relevant to cancer processes
- Sympathetic adrenomedullary system (SAM)
 - catecholamines (and cortisol) decrease production of Th1-cytokines such as γ -IFN and IL-12 and increase production of Th2 cytokines such as IL-10
 - shifts toward Th2 cytokine production have been postulated to promote neoplastic processes.
- Opiate peptides
 - may down-regulate NK cells through their activation of the HPAC system, stimulating the release of ACTH and corticosteroids such as cortisol.
- Neuroactive hormones (ACTH) released by the lymphocytes themselves, which may be active both in the CNS and the periphery

STRESS ACTIVATES THE HPAC AXIS



Psychosocial-Endocrine-Immune Mechanisms In Cancer: *Cortisol*

- animal studies indicated that macrophage and NK activity against tumor growth was inhibited by psychosocial stressor-induced elevations in corticosteroids
- elevated corticosterone (rodent equivalent of cortisol) suppressed IFN production, which is important for augmenting and maintaining NKCC
- corticosteroid inhibitors facilitate resistance to tumor growth in mice

Psychosocial-Endocrine-Immune Mechanisms In Cancer

In humans, psychosocial stressors may relate to the course of breast cancer through *sex hormones* (e.g., estrogens) and "*stress*" hormones (e.g., cortisol) that:

- contribute directly to tumor growth
- SNS-related catecholamines and HPAC-related cortisol may affect disease course in cancer is through their suppressive effects on T-lymphocytes and NKCC

Psychosocial-Endocrine-Immune Mechanisms In Cancer Patients

- Exploring HPAC functioning as a means of explaining relations between psychosocial factors and the course of cancer appears to be an important avenue to pursue
- *Psychosocial interventions* that alter stress responses and levels of HPAC hormones may provide mental and physical health benefits for these people.

Psychosocial Interventions for Cancer Patients

- Facilitating Adjustment to the Cancer Diagnosis
- Optimizing Health Outcomes and Increasing Survival in Cancer Patients

Optimizing *Health Outcomes* and *Increasing Survival* in Cancer Patients

- Reducing cancer initiation/promotion
- Preventing complications after treatment (e.g., immunosuppression, infectious disease and side effects)
- Lengthening disease-free survival by slowing cancer progression

Reducing cancer initiation/promotion

- No studies to date have studied the effects of psychosocial intervention on the initiation/promotion of cancers
- Target populations include high-risk hosts such as:
 - those who are immunocompromised (e.g., those with HIV infection or receiving immunosuppressive therapy after organ transplant),
 - those with a family history of cancer and/or testing positive for markers such as BRCA genes

Reducing cancer initiation/promotion

Specific populations for future studies:

- HIV+ women and men with carcinogenic viral infections (HPV, EBV, HHV-8)
- Men with elevated Prostate Specific Antigen (PSA)
- Women testing positive for BRCA genes
- Men and women with specific form of dysplasia
 - Cervical intraepithelial neoplasia (CIN)
 - Anal intraepithelial neoplasia (AIN)
 - Prostate intraepithelial neoplasia (PIN)
 - Breast dysplasia (carcinoma *in-situ*)

Preventing Complications After Treatment (2 examples)

- 1. Since: both stressors and surgery have been associated with decrements in immune functioning
- Then: stress-reducing psychosocial interventions administered just before surgery might optimize post-surgical immune status thereby possibly the growth of cancer cells mechanically "spread" through the surgical procedure.
- 2. Since: stress is associated with increased susceptibility to upper respiratory infections and bacterial infections and cancer patients, especially those who are emotionally distressed and receiving chemotherapy or other immunosuppressive adjuvant therapies, may be vulnerable to stress-associated opportunistic infections
- Then: stress-reducing psychosocial interventions administered just before surgery might optimize post-surgical immune status thereby possibly reducing the risk of infectious disease, the leading cause of death in CA.

Lengthening Disease-Free Survival

- At least 7 studies using either random assignment or matched controls that have tested the effects of psychosocial interventions on survival in cancer patients
 - three appeared to produce beneficial effects on survival (Speigel et al., 1989; Richardson et al., 1990; Fawzy et al., 1993)
 - four did not (Linn et al., 1982; Gellert et al., 1993; Ilnyckyj et al., 1994; Goodwin et al., 2001)
 - these studies employed follow-up periods ranging from 1 – 11 years and varying disease stages.

Biobehavioral Mechanisms for Health Effects of Psychosocial Interventions

Some have proposed that the factors mediating the health effects of these interventions may be grouped into broad categories:

- +negative health behaviors (e.g., smoking, fat intake)
- positive health behaviors (e.g., diet, exercise, medical adherence)
- modulation of biological systems (e.g., neuroendocrine and immune system)

What evidence suggests that psychosocial intervention can have beneficial immune effects?

- Fawzy et al. (1993): post-surgical early-stage melanoma patients receiving a 6-week group psychosocial intervention showed more use of active coping strategies and increased NKCC compared to those who received surgery plus STD care only
- Schedlowski et al. (1994): decreases in plasma cortisol and increases in circulating lymphocytes in early-stage breast cancer patients after 10-weeks of relaxation and guided imagery.

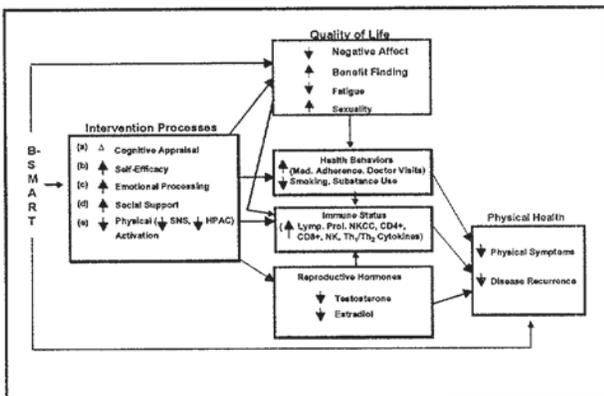
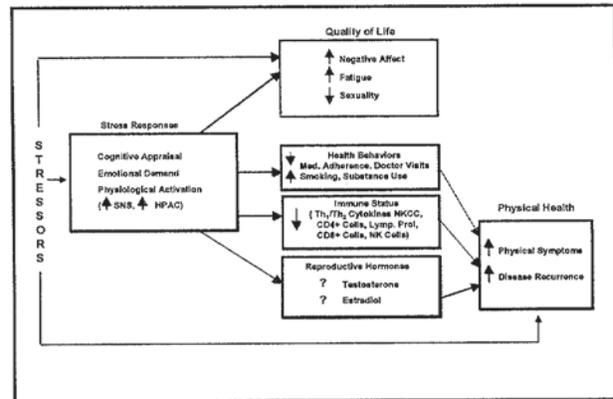
What evidence suggests that psychosocial intervention can have beneficial immune effects?

- Gruber et al (1993) found that 13 early-stage breast cancer patients completing a 9-week stress reduction intervention showed increases in lymphoproliferative responses to PHA and NKCC.
- Andersen et al (1999) found distress reductions and quality of life increases and in NKCC among 100 Stage II and III BRCA pts in an Intervention to reduce stress, enhance QOL, increase positive health behaviors, and decrease negative ones

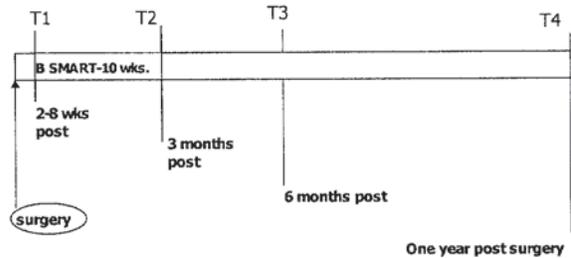
COGNITIVE BEHAVIORAL STRESS MANAGEMENT DECREASES DEPRESSION AND ENHANCES BENEFIT FINDING AND OPTIMISM AMONG WOMEN WITH EARLY-STAGE BREAST CANCER

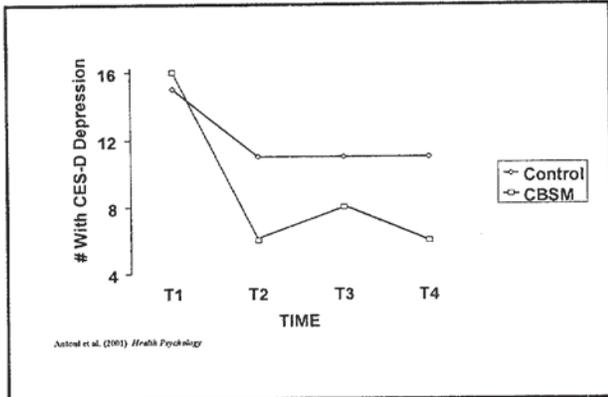
M. Antoni, Ph.D., A. Boyers, Ph.D., K. Kilbourn, Ph.D., S. Alferi, M.S., P. Arena, M.S. and C. Carver, Ph.D.

Department of Psychology
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Coral Gables, FL



Assessment Time Points



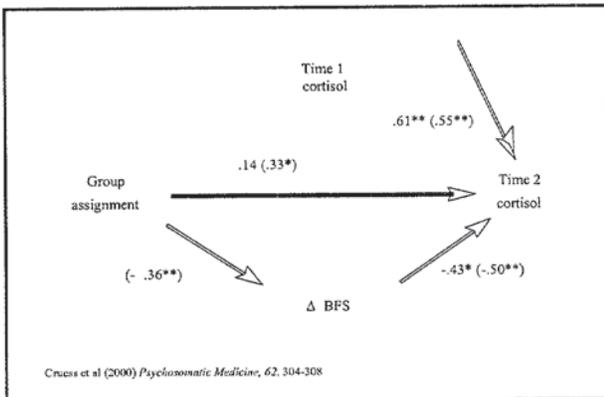
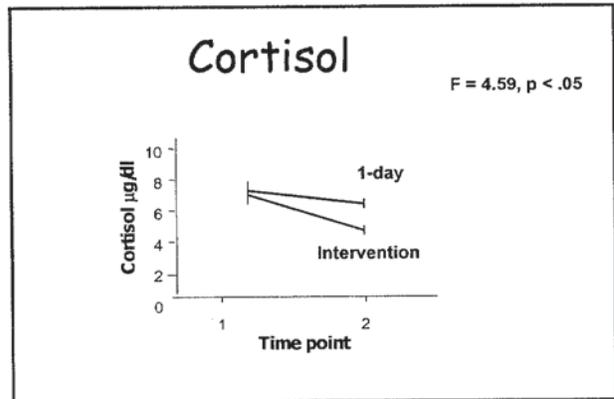
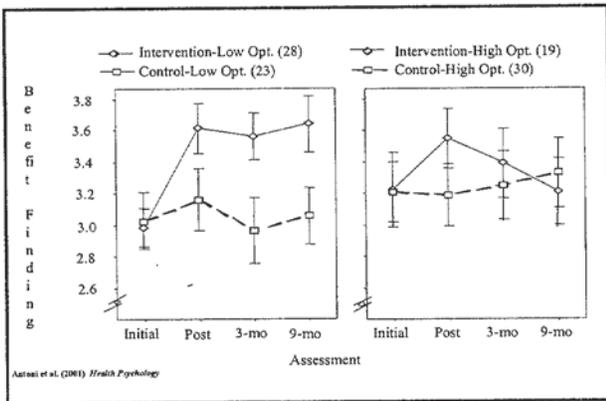


SAMPLE ITEMS ASSESSING BENEFIT FINDING, REGARDING HAVING HAD BREAST CANCER

Having had breast cancer ...

- has taught me how to adjust to things I cannot change.
- has helped me take things as they come.
- has brought my family closer together.
- has made me more sensitive to family issues.
- has taught me that everyone has a purpose in life.
- has contributed to my overall emotional and spiritual growth.
- has helped me become more aware of the love and support available from other people.
- has helped me become more focused on priorities, with a deeper sense of purpose in life.
- has helped me become a stronger person, more able to cope effectively with future life challenges.

Astrol et al. (2001) Health Psychology



What evidence suggests that psychosocial intervention can have beneficial immune effects?

- We found that breast cancer patients assigned to the 10-week CBSM showed significant increases in lymphoproliferative responses (LPR) to anti-CD3 (McGregor et al., 2000).
- Greater increases in benefit-finding (including increased sense of meaning, improved interpersonal relationships, and greater spirituality) during the 10-week intervention period showed greater LPR at 3 months follow-up

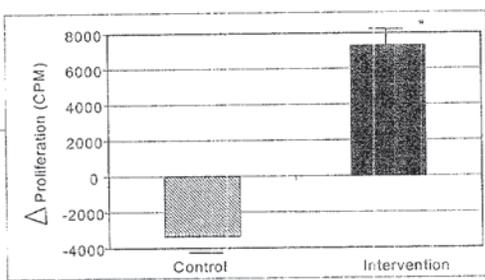


Figure 1. Mean change in proliferative response (counts per minute, CPM) to anti-CD3 (CPM) from T1 to T2 in breast cancer patients assigned to the control vs. CBSM intervention condition. * p<.05

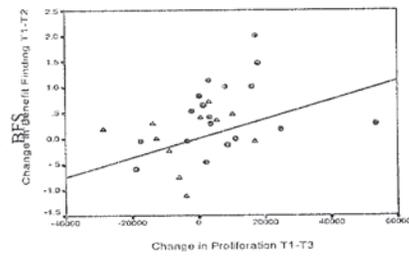


Figure 2. Scatterplot showing correlation between change in proliferative response to anti-CD3 (counts per minute, CPM) and changes in benefit finding among breast cancer patients assigned to the CBSM intervention vs. the control condition.

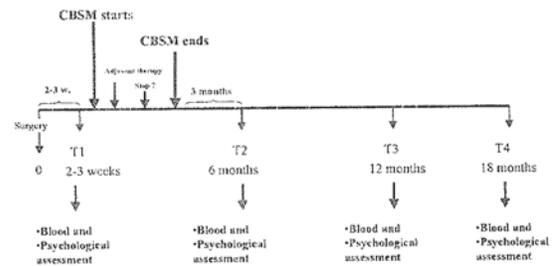
Breast Cancer-Results of First NCITrial

Early stage patients assigned to CBSM showed

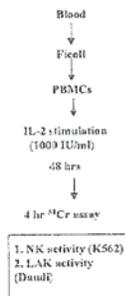
- increases in benefit finding and optimism
- decreased depression
- decreases in plasma cortisol
- increases in lymphocyte proliferation

What Next?

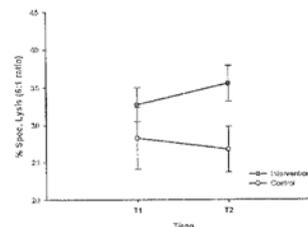
Second NCI Trial Protocol



Cytotoxicity methodology:

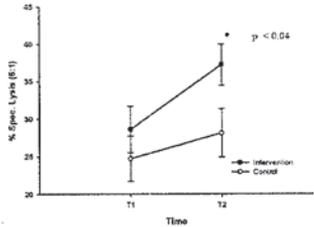


IL-2 activated NK/LAK response to K562



IL-2 activated NK/LAK response to K562 does increase in the Intervention group when compared to Controls. Fresh PBMCs were incubated in the presence of IL-2 (1000 IU/ml) for 48 hours. Specific lysis % was as an effector to target ratio of 6 to 1 against K562. Each point represents the mean value and standard error of the collected data. *Psychosomatic Medicine* 2002, 64, 106.

IL-2 activated LAK response to Daudi



LAK activity increases from T1 to T2 more in the Intervention group than in the Control group from T1 to T2. A total of 26 patients (15 CBSM Intervention, 11 Control). Fresh PBMCs were incubated in the presence of IL-2 (1000 U/ml) for 48 hours. Percentage of specific lysis was at an effector to target ratio of 6 to 1 against Daudi. Each point represents the mean value and standard error. *Psychosomatic Medicine*, 2002, 64, 106.

BFS scores and NK/LAK response to K562

- Women in CBSM with greater increases in BFS scores showed greater increases in NK/LAK response to K562 ($r = 0.45$).

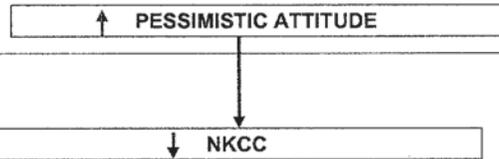
Psychosomatic Medicine, 2002, 64, 106.

Cervical Dysplasia & Stress

Elevated life stress predicts greater promotion and persistence of squamous intraepithelial lesions (SIL), HSV-2 outbreaks, and greater decline in natural killer (NK) cell percentages over a one-year prospective period in women co-infected with HIV and HPV.

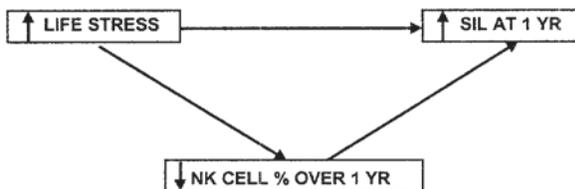
Byrnes, Antoni et al. (1998) *Psychosomatic Medicine*, 60, 714 - 722.
Byrnes-Pereira, Antoni et al. (in press) *Journal of Psychosomatic Research*

Women Living with HIV and HPV: Psychosocial Factors and Immunity



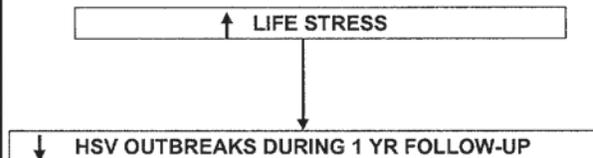
Byrnes, D., Antoni, M. H., et al. (1998). Stressful events, pessimism, and natural killer cell cytotoxicity in HIV+ Black women at risk for cervical cancer. *Psychosomatic Medicine*, 60, 714 - 722.

Women Living with HIV and HPV: Stress, Immunity & SIL Over Time



Byrnes-Pereira, D., Antoni, M.H., et al. (2000). Declines in natural killer cell percentages mediate the effects of high life stress on the incidence of cervical dysplasia in HIV+ Black women at risk for cervical cancer. *Psychosomatic Medicine*, 62, S105.

Women Living with HIV and HPV: Stress & Herpes Simplex Virus (HSV) Outbreaks Over Time



Byrnes-Pereira, Antoni et al (in press) Stress as a predictor of symptomatic genital herpes virus recurrence in women with Human Immunodeficiency Virus. *J. Psychosom Research*

Social Support and Immunity in HIV+ women with HPV

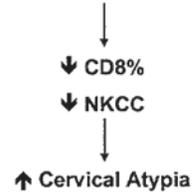
Danielson, Pereira, Antoni, et al. (1999) previously demonstrated relations between social support and immunity in HIV+ women with HPV

Social support was associated with...

- ↑ CD8+CD3+ cell count
- ↑ NKCC

Social Support, Immunity, and CIN in HIV+ women with HPV

↑ Aversive Social Support



Depression & Cortisol in HIV+ Women with HPV

↑ BDI scores associated with ↑ 15-hour urinary cortisol output ($\beta = .68, p < .01$)

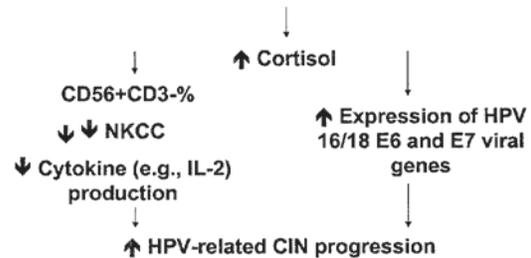
Persisted after controlling for...

- CD4+CD3+ cell count
- Biobehavioral controls
 - Alcohol consumption
 - Nicotine consumption

Ennis, Pereira, Antoni, et al. *Psychosomatic Medicine*, 2002, 64, 113.

Mood Disturbance, Cortisol, & CIN

↑ Depressive symptomatology

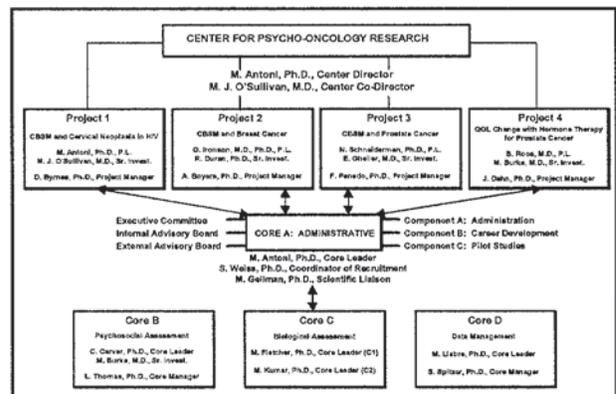


Center for Psycho-Oncology Research

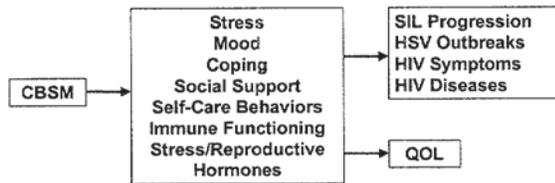


"KEEPING HOPE ALIVE"

■ Cognitive-Behavioral Stress Management (CBSM) Effects on Cervical Neoplasia Among Women Living with HIV



“Keeping Hope Alive”



Formal Screening Visit: Colposcopic Examination

- Pre-Examination:
 - ▮ Education
- Examination:
 - ▮ STD Assessment (e.g., HSV lesions)
 - ▮ Papanicolaou Smear
 - ▮ Cervical Biopsy and Endocervical Curettage
 - ▮ HPV DNA swab
- Post-Examination:
 - ▮ PEAPS-Q-R
 - ▮ \$60 cash payment
 - ▮ Compensation for lunch, transportation, childcare
 - ▮ 15-Hour Urine Collection Instructions
 - ▮ Hybrid Capture II Assay

Study Procedures At A Glance

	T0	T1	T2	T3	T4
When		T0 + 2 wks	T1 + 10 wks	T2 + 6 mos	T3 + 6 mos
Screen	X				
Psych		X	X	X	X
Blood		X	X	X	X
Urine		X	X	X	X
Colpo	X			X	X

T0 = Formal Screen

Health Indicators in Cancer Promotion

(Eg. Cervical Neoplasia)

- Clinical indicators
 - SIL
 - Invasive Cx cancer
 - HSV-2 outbreaks
- Viral indicators
 - HIV load
 - HPV load

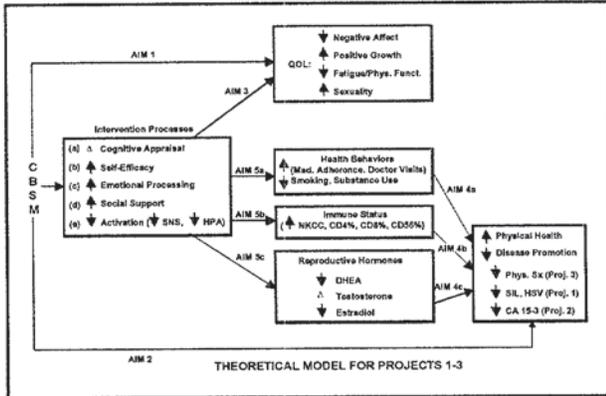
Health Indicators in Cancer Promotion

(Eg., Cervical Neoplasia)

- Immune indicators
 - CD4, CD8, NK
 - HSV-2, IgG, HPV, IgG
 - NKCC and LAK
 - CTL to HPV
 - Perforin and Granzymes in NKCC, CTL
 - T_{h1}/T_{h2} cytokines after anti-CD3

Neuroendocrine Outcomes

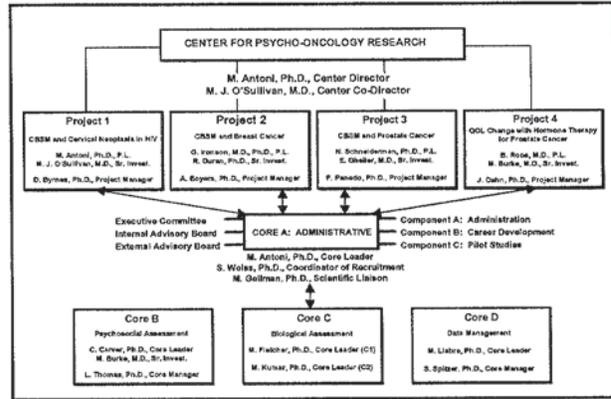
- URINE
 - ▮ Norepinephrine
 - ▮ Epinephrine
 - ▮ Cortisol
 - ▮ Creatinine
- SERUM
 - ▮ DHEA-S
 - ▮ Free testosterone
 - ▮ Estradiol
 - ▮ Progesterone



This NIH P50 includes:
4 Major Randomized Trials
5 Core Laboratories
A Pilot Project Research Program

Our P50 stands at the heart of our NCI-funded Psycho-Oncology research program flanked by two NCI R01s both focused on biobehavioral factors in breast cancer survivorship:

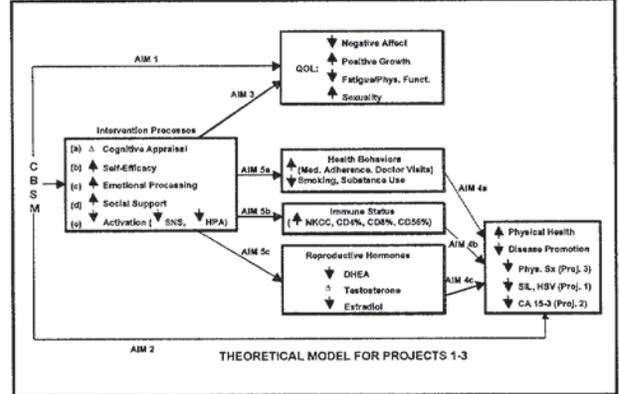
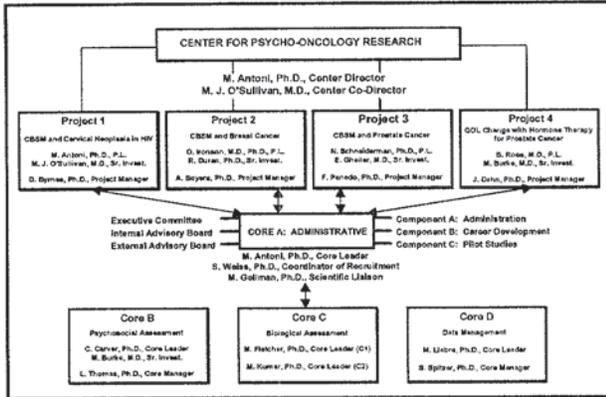
IP50	CPOR	N = 750	1999-04
IR01	CBSM effects after surgery	N = 200	1999-04
IR01	Predictors of long-term survival	N = 500+	1999-04



The CPOR has funded a total of 9 pilot projects since its inception, including awards to established basic scientists wishing to conduct translational clinical research in oncology

Bonnie Blomberg, Ph.D., Associate Professor of Microbiology/Immunology

■ Pilot study: Effects of stress management on the production of Th1 (IL-2, IL-12, and IFN- γ) and Th2 (IL-5, IL-10) cytokines in women with Stage 1-3 breast cancer during the weeks after surgery



PSYCHOLOGICAL DISTRESS IN PROSTATE CANCER (CaP)

Despite high survival rates for early stage CaP, treatment side effects such as urinary incontinence and ED can further compromise quality of life and lead to psychological distress states

PSYCHOLOGICAL DISTRESS IN PROSTATE CANCER

Because CaP is primarily a disease of older men, possible chronic stressors associated with aging (co-morbidity, social isolation, retirement, caregiving, financial burdens) can cause further psychological distress

PNI MECHANISMS IN PROSTATE CANCER

Chronic Psychological Stress:

decreased blood flow and \leftrightarrow lymphocytic infiltration of the prostate in rats

increased serum catecholamines & neuropeptide Y

Neuropeptide Y is the most abundant neuropeptide in prostatic autonomic nerves & is co-released with catecholamines

PNI MECHANISMS IN PROSTATE CANCER

Testosterone

•Increased circulating testosterone in conjunction with sex hormone binding globulin is associated with risk of CaP

•Elevated levels may be associated with stress-related HPAC dysregulation

PNI MECHANISMS IN PROSTATE CANCER

Testosterone

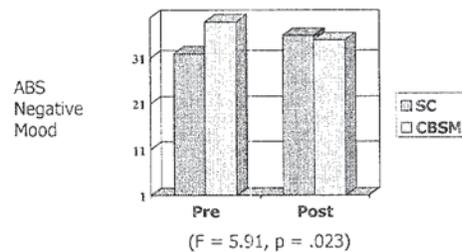
• Our CBSM intervention has normalized free testosterone levels among men and women in parallel with reductions in negative mood state

Cruess, Antoni et al., (2000) Health Psychology; Cruess, Antoni et al. (2001) Int J Beh Med

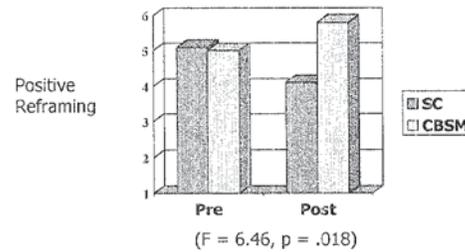
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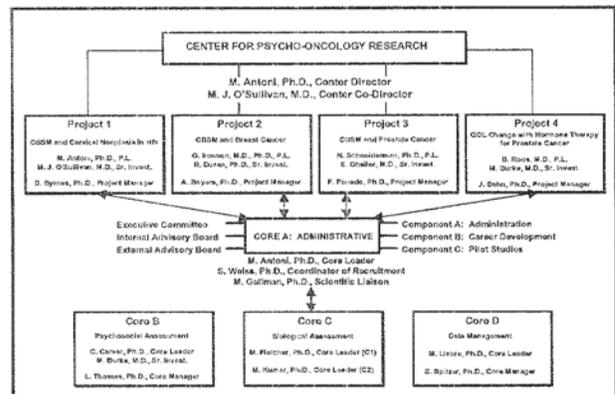
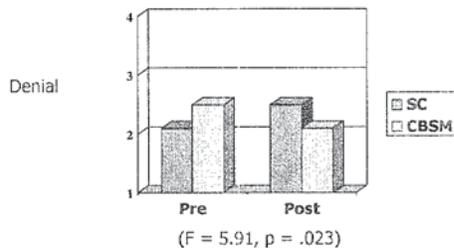
Prostate Cancer
Pre to Post CBSM Changes in ABS Negative Mood



Prostate Cancer
Pre to Post CBSM Changes in Positive Reframing



Prostate Cancer
Pre to Post CBSM Changes in Denial



Limitations of Cancer Intervention Studies Conducted To Date. *What's Next?*

All focused on non-specific indices of immune system status, which make it difficult to draw conclusions about prospective mechanisms of immune system regulation

- how do cell-signaling cytokines relate to psychosocial changes during intervention?
- are findings specific to certain antigens related to specific cancers?
- the health relevance of intervention-related immune changes needs to be determined.