

Kræft er stressende

Om sammenhænge mellem stress og kræft


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DEPT. OF ONCOLOGY - AARHUS UNIVERSITY HOSPITAL - DEPT. OF PSYCHOLOGY - AARHUS UNIVERSITY

Temaer

- Betydning af stress for kræftrisiko?
- Betydning af stress for kræftprognose?
- Mulige mekanismer?
- Intervention?



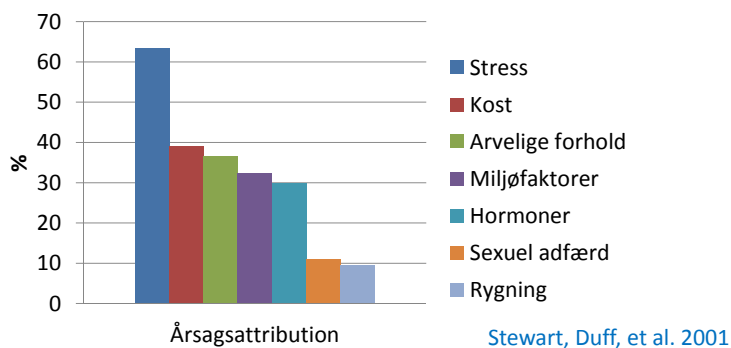
Zachariae

Forestillinger om sammenhænge

- Når personer udvikler kræft, vil de fleste lede efter forklaring: hvor fik jeg kræft?
- Forskning tyder på
 - Årsagsattribution varierer
 - Hænger sammen med socioøkonomisk status
 - Årsagsattribution påvirker patientens
 - Mestringsstrategier
 - Psykiske tilstand (angst, depression)
 - Sundhedsadfærd

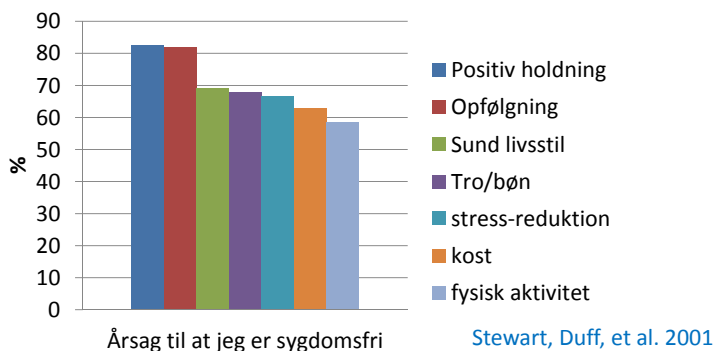
Forestillinger om stress og kræft

- Årsagsattribution blandt sygdomsfri kvinder behandlet for ovariecancer:



Forestillinger om stress og kræft

- Årsagsattribution blandt sygdomsfri kvinder behandlet for ovariecancer:



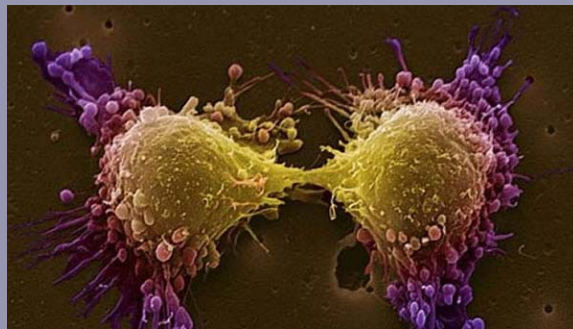
Forestillinger om stress og kræft

- Kvinder med brystkræft:
 - 42% mente at **stress** var årsag til deres kræft og 60% mente at positiv holdning forebyggede recidiv (Stewart et al. 2001)
 - 58,1% mente at **stress** var årsag til deres kræft. De havde lavere psykisk velbefindende og var mere tilbøjelige til at have gennemført livsstilsændringer siden diagnosen (Panjari et al. 2012)
 - Forestillinger om at deres kræft skyldtes miljø-faktorer, arvelige faktorer og stress var forbundet med større **angst** for tilbagefald. (Dumalaon-Canaria et al. 2016)

Forestillinger om stress og kræft

- Mænd med testikelkræft:
 - 28% oplevede angst for tilbagefald. Angst for tilbagefald var forbundet med øget depression og forestillinger om at **stress** var en medvirkende årsag til kræftsygdommen. (Pedersen et al. 2012)
- Befolkningen:
 - Lavere uddannelsesniveau forbundet med mindre tiltro til at tro på, at kræft kan helbredes og mindre viden om betydning af tidlig diagnose (Schernhammer et al. 2010)
 - Holdninger påvirkes af traditionelle og sociale medier

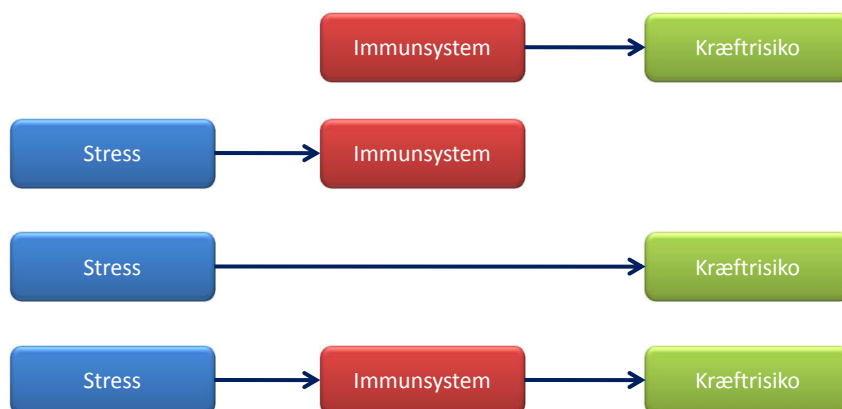
STRESS - BETYDNING FOR KRÆFTRISIKO?

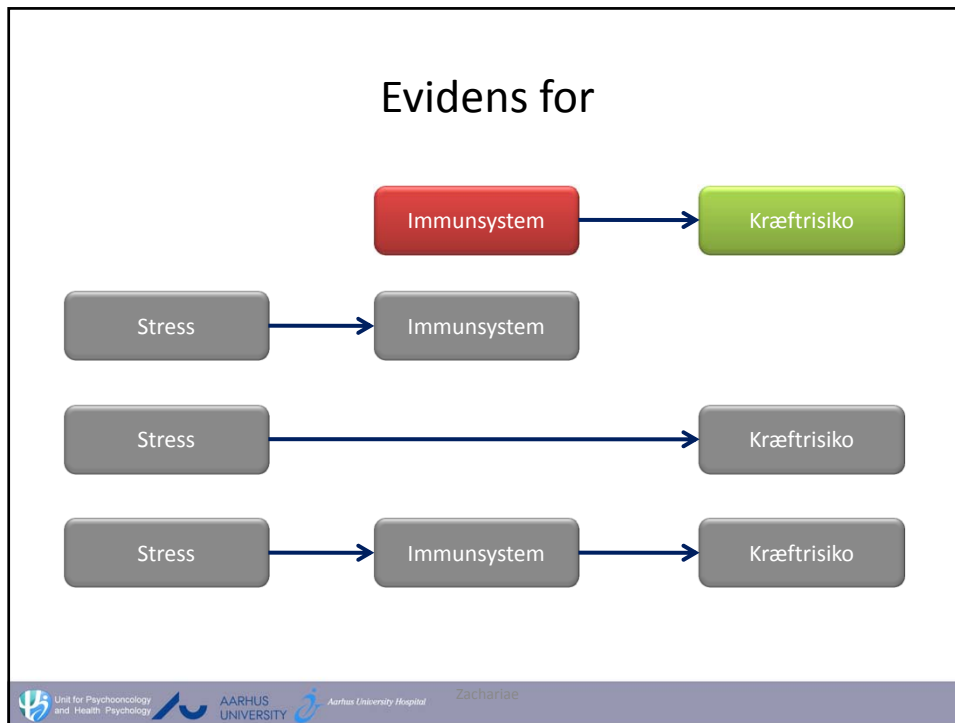


Plausible mekanismer

- Hvis vi skal acceptere, at psykosociale faktorer, f.eks. *stress*, skal kunne influere på kræft-risiko, skal vi kunne identificere plausible *mekanismer*
- Mulige mekanismer
 - Direkte mekanismer, f.eks. hormon og immunsystem
 - Indirekte mekanismer, f.eks. sundhedsadfærd

Der skal være evidens for





Immun-redigering

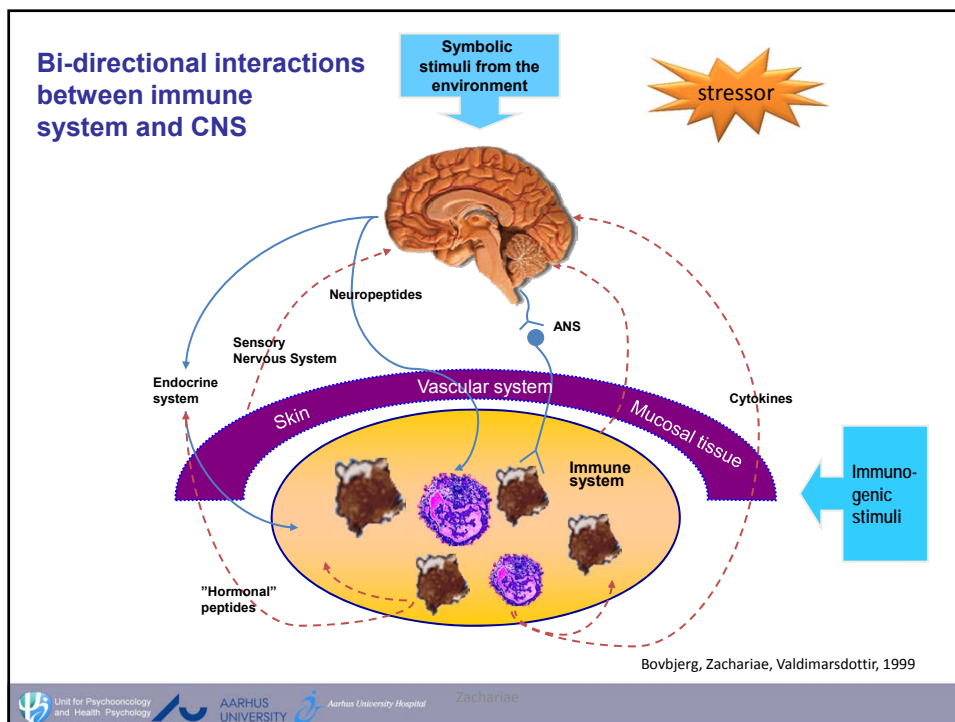
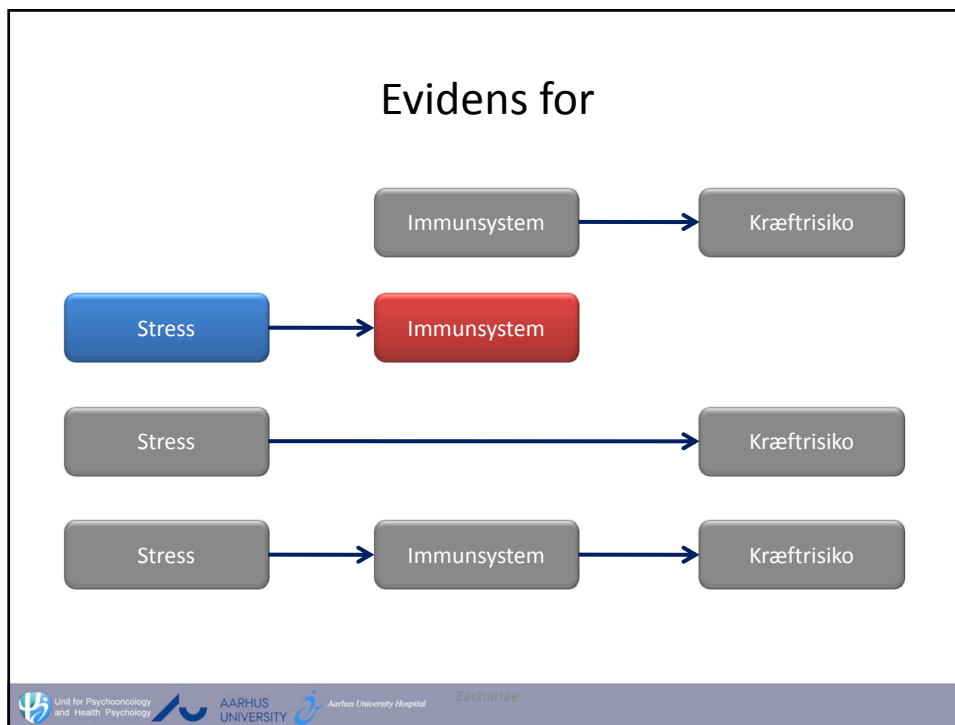
- Aktuelt antages tre faser i udvikling af kræft: **Elimination**, **Equilibrium**, og tumor **Escape**. Den tredje fase etableres gennem *immunologic sculpting*, dvs. naturlig selektion af celler, der er mindre immunstimulerende. STRESS? Dunn et al. 2002; Teng et al. 2008)

a) Elimination **b) Equilibrium** **c) Escape**

Tumor-escape mekanismer: a) ikke-immunogene varianter, b) immun-undertrykkende varianter, c) angiogenese-fremmende varianter

Müller et al. 2002; Piemonti et al. 2003

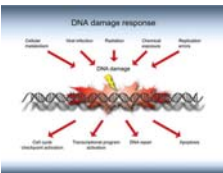

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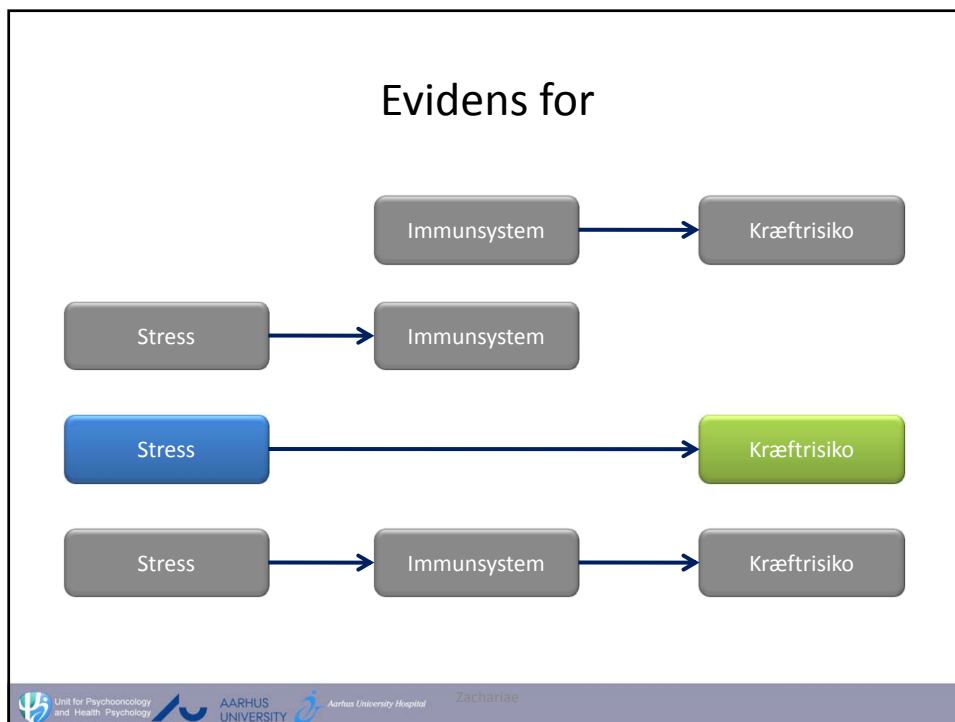
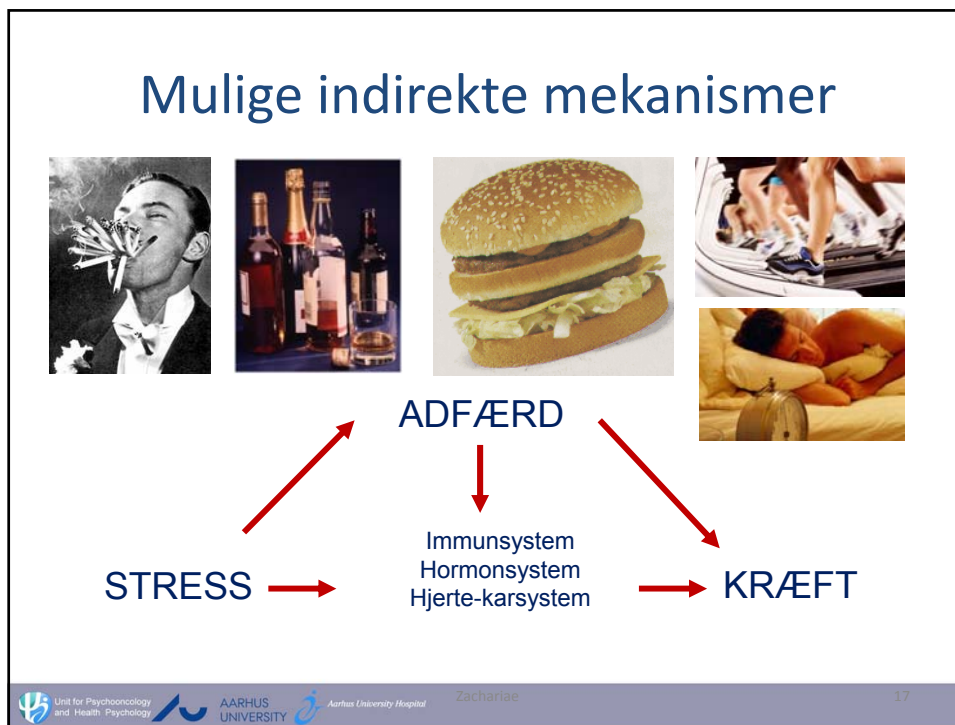


Stress -> inflammation -> kræft

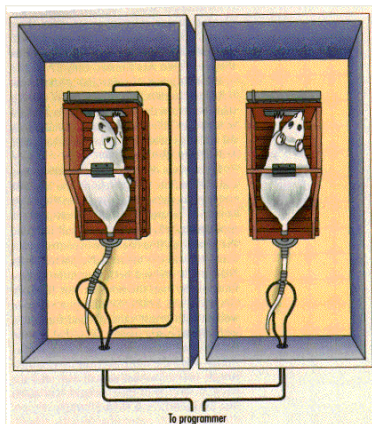
- DNA-skader kan føre til øget kræftisiko hvis det beskadigede DNA ikke bliver repareret eller fjernet af kroppens DNA reparationsmekanismer
 - Stresshormoner (adrenalin, noradrenalin, kortisol) forbundet med DNA-skader (Flint et al. 2007; Jørgensen et al. 2011)
 - Post-traumatisk stress (PTSD) forbundet med øget udskillelse af proinflammatoriske cytokiner (Gill et al. 2008, 2009)
 - Proinflammatoriske cytokiner forbundet med DNA-beskadigelse (Jaiswal et al. 2000)
 - Kronisk inflammation og oxidativ stress forbundet med aldringsrelaterede sygdomme, fx kræft (Khansari et al. 2009)
 - Kortere telomerer forbundet med kræftisiko (Zhu et al. 2016)
 - Stress forbundet med øget telomerforkortelse og stressreduktion forbundet med langsommere telomerforkortelse (Eisenberg, 2011; Epel, 2004; Antoni et al. 2012; Dahlggaard & Zachariae, 2014)
 - Stress forbundet med lavere niveau af DNA-reparation (Kiecolt-Glaser et al. 1985; Cohen et al. 2000; Baum et al. 2007; Jørgensen, 2013)


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Eksperimentelle modeller



Ikke-kontrollerbar stress har vist sig at:

Hæmme cellulær immunfunktion

Fremme vækst af transplanterede tumorer

Reviews: Riley, 1979; Nieburgs et al. 1979; Sklar & Anisman, 1981; Irwin & Anisman, 1984; Justice, 1985; Vogel & Bower, 1991;

Meta-analyse (142 prospektive undersøgelser) af stress-relaterede faktorer og kræftisiko (alle kræfttyper)

Chida et al. 2008

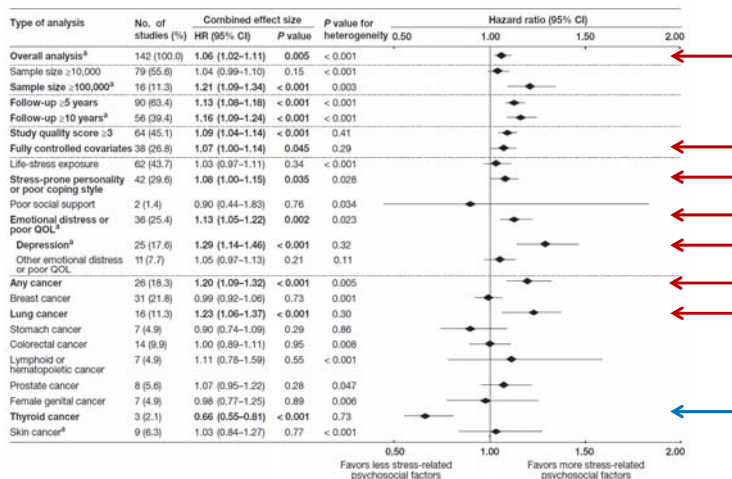
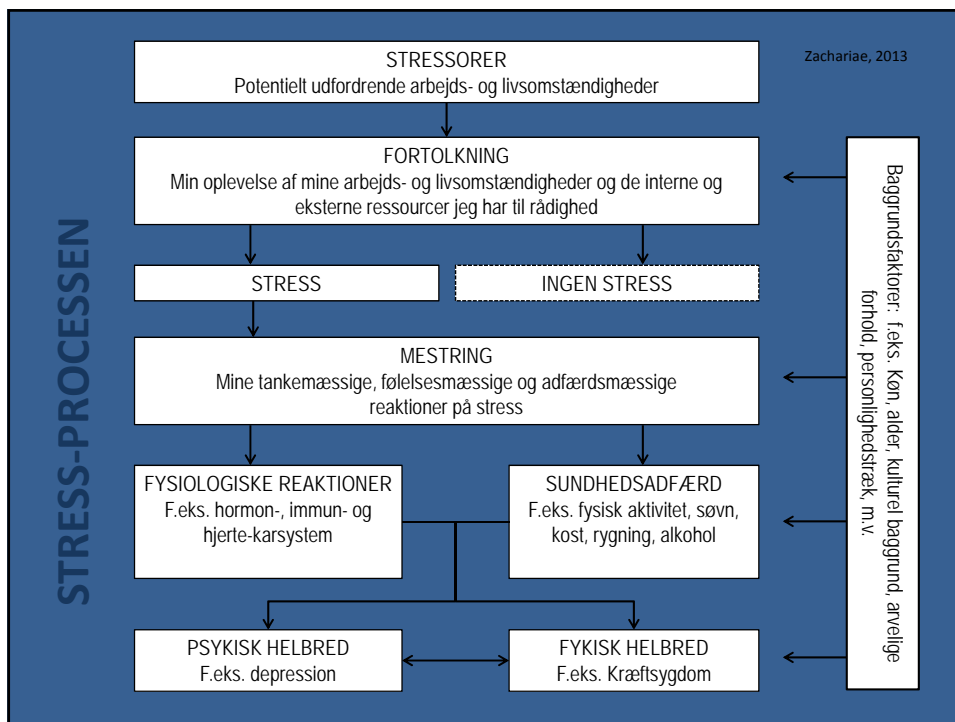
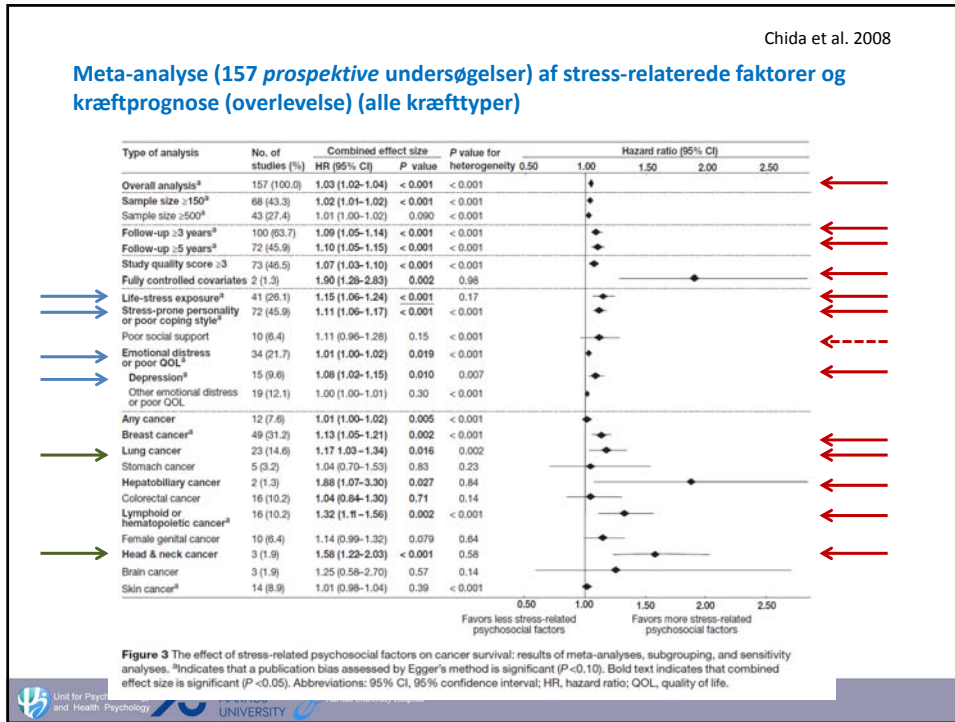


Figure 2 The effect of stress-related psychosocial factors on cancer incidence: results of meta-analyses, subgrouping, and sensitivity analyses. ^aIndicates that a publication bias assessed by Egger's method is significant ($P < 0.10$). Bold text indicates that combined effect size is significant ($P < 0.05$). Abbreviations: 95% CI, 95% confidence interval; HR, Hazard Ratio; QOL, quality of life.



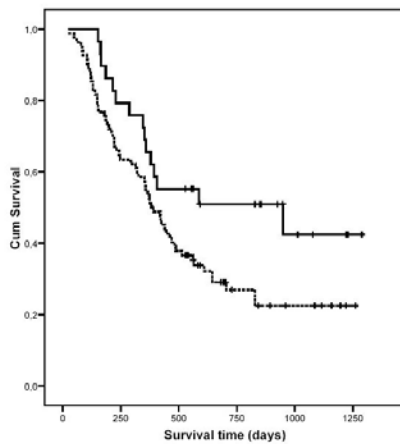
Stress og kræftprognose





Stress og overlevelse blandt lunge, blære og ovariecancerpatienter Medieres af øget antal neutrofile celler (inflammatorisk markør)

N: 114



Influence of stress partly mediated by neutrophil cell count (High neutrophil-counts = inflammation = increased risk of infection and reduced survival)

Correlation between survival and neutrophil count in cancer patients (Ovarian, lung, and melanoma)

| | Neutrophil count Before treatment (T1) (N=114) | Neutrophil count During treatment (T2) (N=114) | Neutrophil count During treatment (T3) (N=107) |
|-----------------|--|--|--|
| Survival (days) | -0.42 ** | -0.26 ** | -0.33 ** |

** $p < 0.01$ (two-tailed) (Pedersen, Zachariae et al. submitted)

Pedersen, Zachariae et al.

Self-efficacy som moderator af stress-prognose-sammenhængen

- Et mål for *forventning* om fremtidig *mestrings-evne*
- ”Min tro på mine evner til at organisere og udføre de handlinger, som er nødvendige for at opnå et bestemt resultat”
(Bandura, 1977;1997)
- Self-efficacy er domæne-specifikt



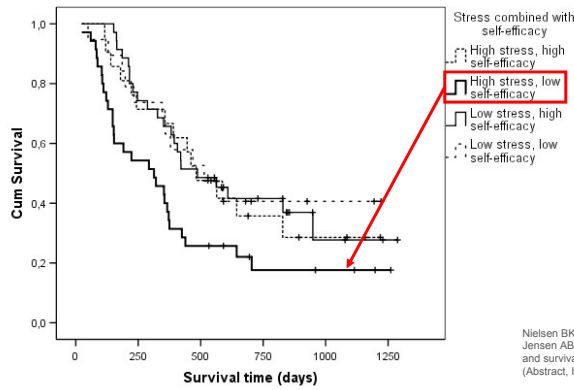
Kræft-relateret self-efficacy

I hvor høj grad er du sikker på, at du vil kunne:

| | |
|--|-------------------|
| 1 Opretholde din egen selvstændighed | 1 2 3 4 5 6 7 8 9 |
| 2 Opretholde et positivt syn | 1 2 3 4 5 6 7 8 9 |
| 3 Opretholde et humoristisk syn | 1 2 3 4 5 6 7 8 9 |
| 4 Udtrykke negative følelser om kræft | 1 2 3 4 5 6 7 8 9 |
| 5 Skubbe tankerne om sygdommen til side, når det er nødvendigt | 1 2 3 4 5 6 7 8 9 |
| 6 Opretholde dine arbejdsaktiviteter | 1 2 3 4 5 6 7 8 9 |
| 7 Forblive afslappet under behandlingerne og ikke blive oprevet af skræmmende tanker | 1 2 3 4 5 6 7 8 9 |
| 8 Aktivt deltage i beslutningerne omkring din behandling | 1 2 3 4 5 6 7 8 9 |
| 9 Stille lægerne spørgsmål | 1 2 3 4 5 6 7 8 9 |
| 10 Søge trost | 1 2 3 4 5 6 7 8 9 |
| 11 Dele bekymringer med andre | 1 2 3 4 5 6 7 8 9 |
| 12 Håndtere kvalme og opkastninger | 1 2 3 4 5 6 7 8 9 |
| 13 Håndtere fysiske forandringer | 1 2 3 4 5 6 7 8 9 |
| 14 Forblive afslappet, hvis du venter en time eller mere på din aftale med lægen | 1 2 3 4 5 6 7 8 9 |

Self-efficacy, stress og prognose

Stress, self-efficacy, and survival



Nielsen BK, Pedersen AF, Vaeth M, Jensen AD, Zachariae R. Perceived stress and survival in cancer: a prospective study (Abstract, ICBM 2008).

Personale-patient relationen

Resultater fra 454 læge-patient-konsultationer:

Læge-patient-relationen har betydning for patient-tilfredshed og forandringer i psykisk velbefindende og kræft-relateret self-efficacy

Association of perceived physician communication style with patient satisfaction, distress, cancer-related self-efficacy, and perceived control over the disease

N. Zachariae^{1,2}, CG Pedersen^{1,2}, AB Jensen¹, E Eberhardt¹, PB Rosen¹ and H von der Maas¹
¹Psychology Research Unit, Aarhus University Hospital, Aarhus, Denmark; ²Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

The aim of the study was to investigate the association of physician communication behaviors as perceived by the patient with patient reported satisfaction, distress, cancer-related self-efficacy, and perceived control over the disease in cancer patients. Questionnaires measuring distress, self-efficacy, and perceived control were completed prior to and after the consultation by 454 patients attending an oncology outpatient clinic. After the consultation, the patients also rated the physician's communication behaviors by completing a patient-physician relationship inventory (PRFI), and the physicians were asked to estimate patient satisfaction. The overall results showed that higher PRFI scores of physician communication and empathy were associated with greater patient satisfaction, increased self-efficacy, and reduced emotional distress following the consultation. In contrast, lower PRFI scores were associated with reduced ability of the doctor to estimate patient satisfaction. The study confirms and expands previous research on the association between physician communication style and patient outcomes.

| Oncologist Communication style | Satisfaction with contact | Satisfaction with medical aspects | Change in distress | Increase in cancer-related self-efficacy |
|--------------------------------|---------------------------|-----------------------------------|--------------------|--|
| Attentiveness | 0.68** | 0.64** | -0.13 | 0.27** |
| Empathy | 0.38** | 0.32** | -0.28** | 0.18** |

Stress -> PTSD -> depression

- **4917 women**
 - 3343, 68% at 3 mo.; 94% of these at 15 mo.
- **Depressive symptoms, 3 months**
 - **13.7%** had depressive symptoms indicating MD
 - **Predictors:** Low SES, comorbidity and psychiatric history. Nodal status only clinical cancer predictor.
- **Cancer-related post-traumatic stress, 3 and 15 months**
 - IES scores suggesting severe PTSD (IES>35):
 - 3 months: **20.1%**
 - 15 months: **14.3%**
 - **Predictors at 15 mo. (adjusted for baseline):** Low SES, previous physical and mental illness, nodal status, physical function at 3 mo.

Prevalence and risk of depressive symptoms 3-4 months post-surgery in a nationwide cohort study of Danish women treated for early stage breast-cancer

Søren Christensen · Robert Zachariae · Anders Sunde Jensen · Michael Vebb · Susanne Melbye · Jørgen Knudsen · Hans von der Maase

Published online: 19 February 2008
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Abstract Background Elevated levels of depressive symptoms are generally found among cancer patients, but studies have primarily focused on cancer-related risk factors. We study the prevalence of depressive symptoms and major depression 3 months following surgery for breast cancer, and for identify clinical risk factors which adjusting for pre-cancer sociodemographic factors, comorbidity, and psychiatric history. **Patients and methods** The study cohort consists of 4917 Danish women, aged 18-70 years, receiving mastectomy treatment for early stage invasive breast cancer during the 7-17 year interval between two national questionnaires. The Danish Breast Cancer Cooperative Group (DBCG) and the surgical department provided baseline information concerning sociodemographic and psychiatric history, and identified three national longitudinal registers. **Results** The results indicated an increased prevalence of depressive symptoms and major depression (13.7%), compared to population-based register. The pre-cancer variables: social status, net wealth, ethnicity, comorbidity, psychiatric history, and for some of independent risk factors for depressive symptoms. Of the clinical variables, nodal status was associated to depression. The Danish Breast Cancer Cooperative Group (DBCG) and the surgical department provided baseline information concerning sociodemographic and psychiatric history, and identified three national longitudinal registers. **Results** The results indicated an increased prevalence of depressive symptoms and major depression (13.7%), compared to population-based register. The pre-cancer variables: social status, net wealth, ethnicity, comorbidity, psychiatric history, and for some of independent risk factors for depressive symptoms. Of the clinical variables, nodal status was associated to depression.

Breast Journal of Cancer (2008), 1, 4
www.springerlink.com

Full Paper
How traumatic is breast cancer? Post-traumatic stress symptoms (PTSS) and risk factors for severe PTSS at 3 and 15 months after surgery in a nationwide cohort of Danish women treated for primary breast cancer

H. G. Christensen^{1,2}, S. Christensen¹, A. S. Jensen¹, S. Melbye¹ and R. Zachariae¹

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Introduction The burden of cancer-related post-traumatic stress (PTSS) is well documented. However, the prevalence of post-traumatic stress symptoms (PTSS) among women with breast cancer (BC) remains unclear. Our primary aim was to explore the prevalence of and risk factors for cancer-related PTSS in a nationwide population-based cohort of women treated for primary breast cancer. **Methods** In all, 4917 of Danish women treated surgically for primary breast cancer between October 2001 and March 2004 completed a questionnaire at 3 months post-surgery (n = 2474), which included the report of being a patient in the Danish National Cohort Study (DNCS), a large-scale, population-based, longitudinal study of 5 million Danes. Data on pre-cancer sociodemographic, comorbidity, and psychiatric history were obtained from the DNCS. Data on post-cancer sociodemographic, comorbidity, and psychiatric history were obtained from the Danish Longitudinal Register (DLR), a large-scale, population-based, longitudinal register on Danish citizens, including sociodemographic, comorbidity, and psychiatric history. **Results** At 3 months post-surgery, 20.1% had IES scores suggesting severe PTSS (n = 975), compared with 14.3% at 15 months (n = 667) with severe PTSS. A 15-month follow-up was associated with a 10% reduction in the prevalence of severe PTSS. **Conclusions** The prevalence of severe PTSS is high among breast cancer patients, and high rates among women reporting post-traumatic stress symptoms (PTSS) were found. Risk factors for severe PTSS, from baseline (pre- and post-surgery) were: low SES, previous physical and mental illness, nodal status, and physical function at 3 months.

Keywords post-traumatic stress symptoms; breast cancer; PTSD; breast cancer; patient quality; prospective studies

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Depression and prognosis

- **4917 women**
 - 3343, 68% at 3 mo.; 94% of these at 15 mo.
 - Followed for up to 13 years
 - Data obtained from national registries
- **Mortality**
 - BDI ≥ 17 (Major depression) at 15 months: 27.1%
 - BDI < 17: 19.6%
 - RR: 1.54 (95%CI: 1.23-1.92)
 - BDI depressive symptom scores (RR per point on the BDI):
 - All cause mortality: 1.015
 - Cancer mortality: 1.019
 - Breast cancer mortality: 1.018
 - Depression at 3 mo. not associated with mortality

Kaplan-Meier survival estimates

Overall Survival (age-adjusted)

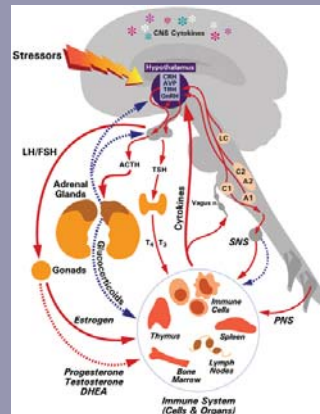
Hazard ratio

BDI Total score 15 mth postsurgery

— HR Linear pred
— HR Spline
- - - HR (95% CI)

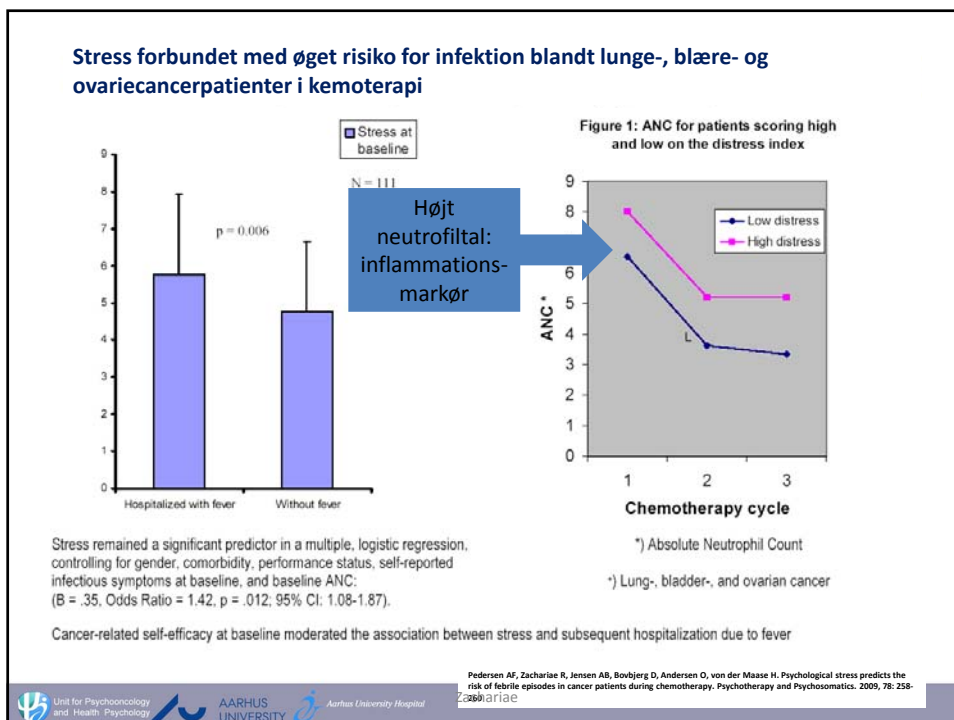
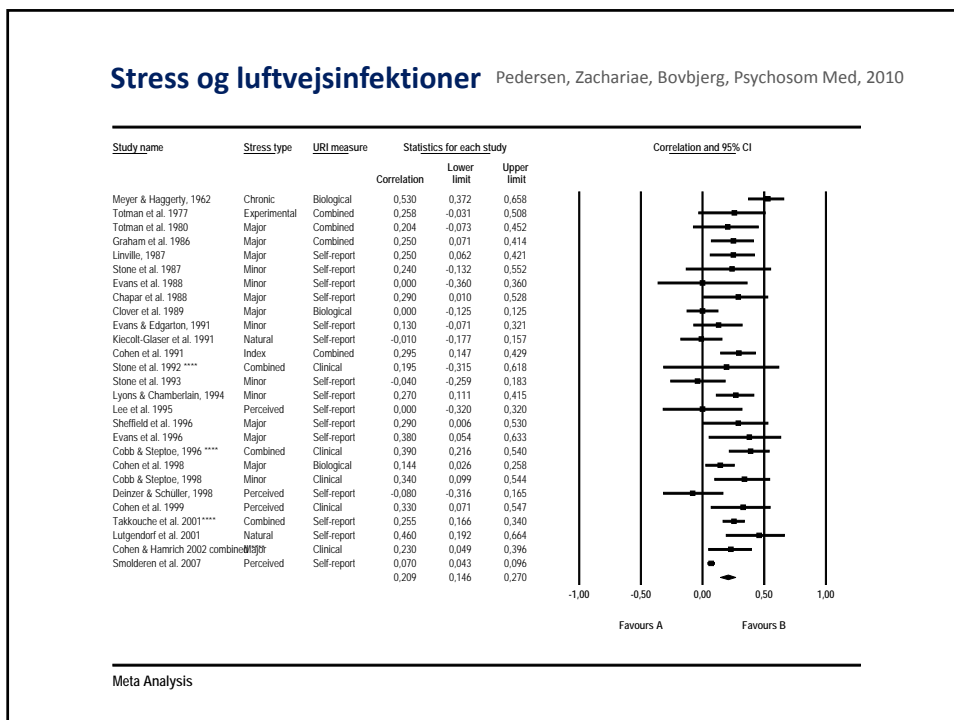
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Mulige mekanismer



Stress->immunitet->infektion->kræft

- Effekter af kronisk stress (> 1 måned) forbundet med øget modtagelighed for eksperimentelt induceret forkølelse. (Cohen et al. 1991, 1998)
- Socio-økonomisk status forbundet med risiko for infektioner i barndommen (Cohen et al. 2004)
- Mulige sammenhænge mellem infektion og kræft
- **Hvor god er evidensen?**
- Meta-analyser peger på at stress er forbundet med:
 - Øget risiko for infektioner (luftvejsinfektioner/HSV)
 - Øget risiko for at udvikle viralt inducerede kræftformer
- Et enkelt studie peger på at stress er forbundet med
 - Øget risiko for at få infektion i forbindelse med kræftbehandling



Stress og HSV udbrud

Y. Chida, X. Mao / Brain, Behavior, and Immunity 23 (2009) 917–925

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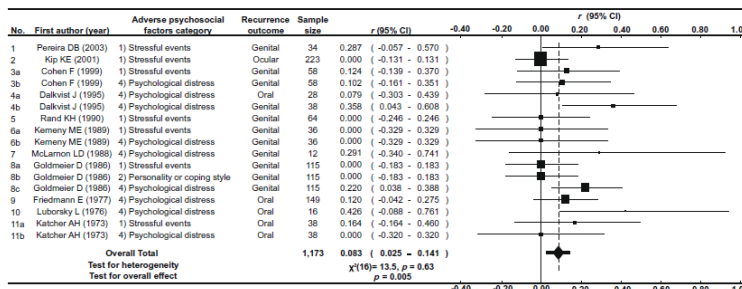
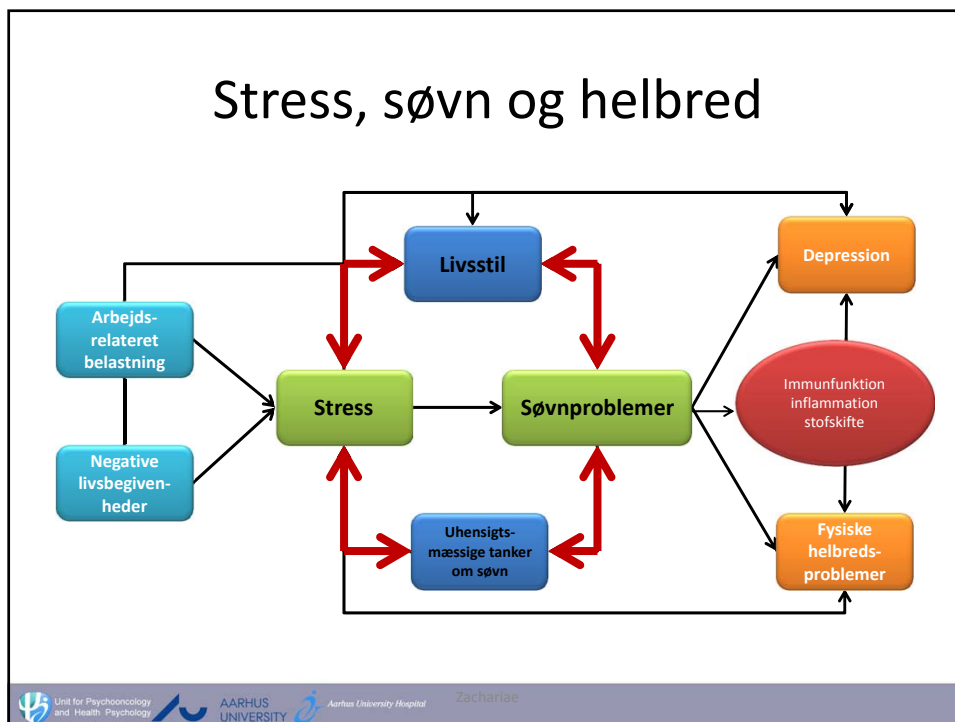
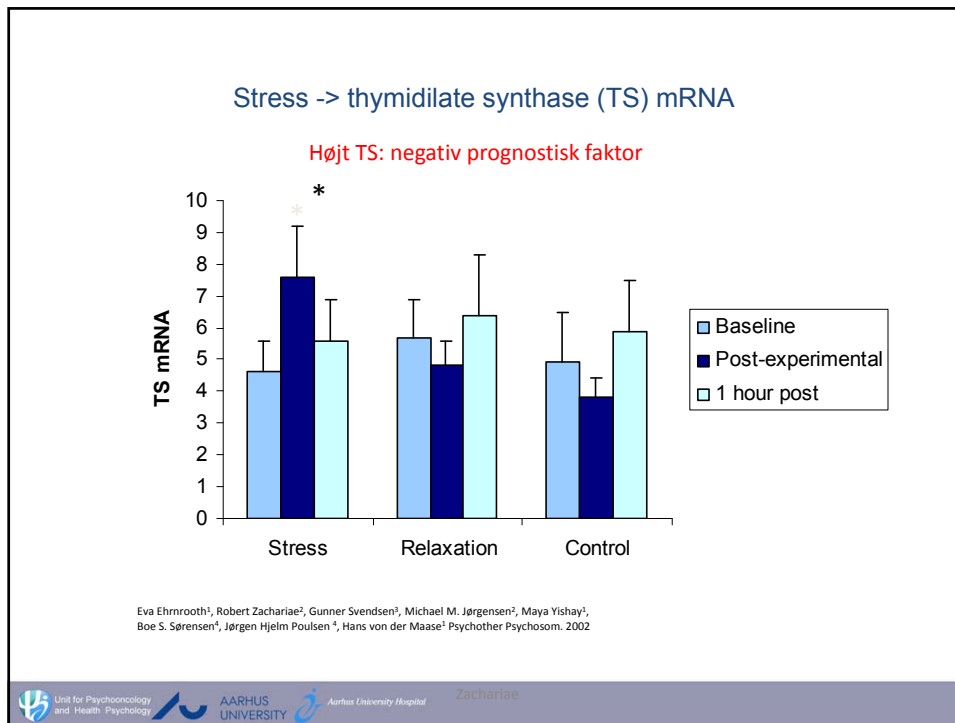
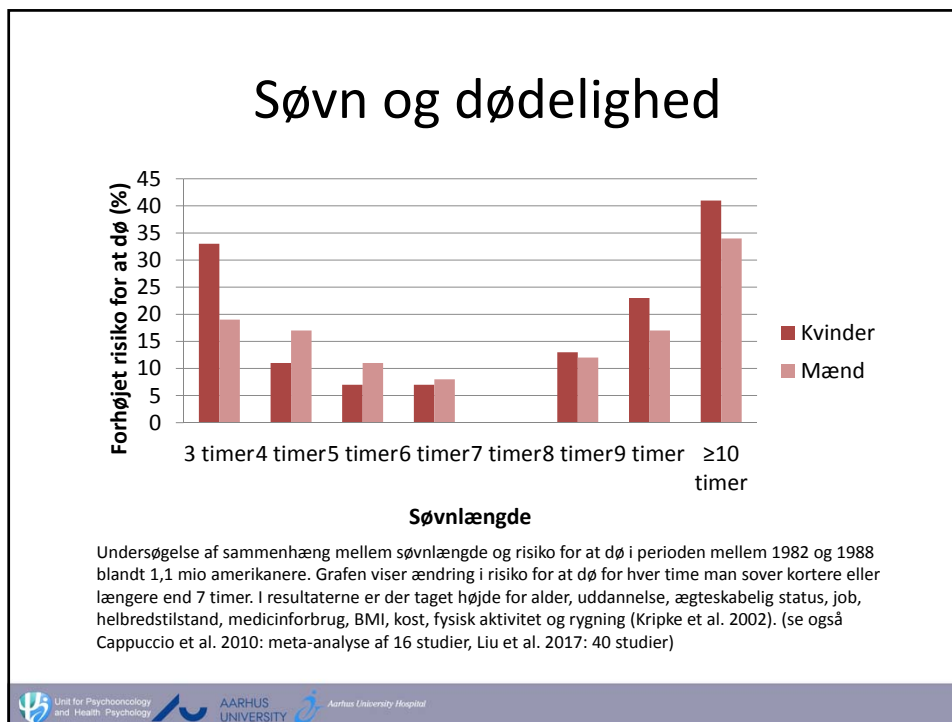


Fig. 2. Forest plots of individual studies investigating the association between psychological stress and symptomatic HSV recurrence. r, correlation coefficient; 95% CI = 95% confidence interval. Higher positive correlation coefficients indicate a more detrimental role of psychosocial stress in HIV disease progression. Individual study symbols are proportional in size to study weights. Studies are only included for which effect sizes could be computed.

Stress -> infektionsrelaterede kræftformer

- **EBV-related**
 - NS
 - **HPV/HCV-related**
 - Liver (RR: 1.14)
 - **HPV-related**
 - Cervical (RR: 1.46)
 - Vulva /vaginal (RR: 1.24)
 - Anal (RR: 1.26)
 - **Total infection-related cancer**
 - RR: 1.17 (1.09 – 1.25) (N: 857/37.208)
- Fang et al. 2011: Loss of a child and infection-related cancers, Sweden 1990-2004





Søvnproblemer, tilbagefald og dødelighed

- To kohortestudier med brystkræft-overleverere:
 - Øget dødelighed (N=3682, 30 år follow-up):
 - Søvnforstyrrelser: HR: **1.49**
 - Meget lang søvn: HR: **1.34**
 - Brystkræft tilbagefald (N=3047. 15 år followup)
 - Varierende søvnlængde (skifter mellem alm og lang) forbundet med tilbagefald (HR: **1.60**), kræft-specifik dødelighed (HR: **1.70**) og dødelighed (alle årsager) (HR: **1.47**)
 - Stabilt søvnmønster (kort og lang): n.s.

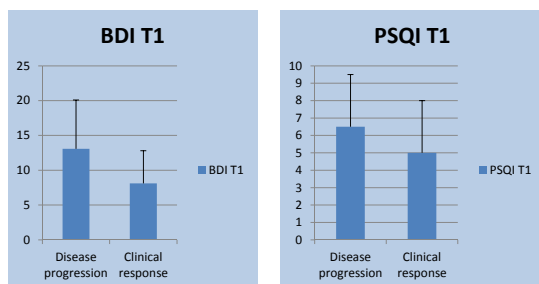
Trudel-Fitzgerald et al. 2017; Marinac et al. 2017

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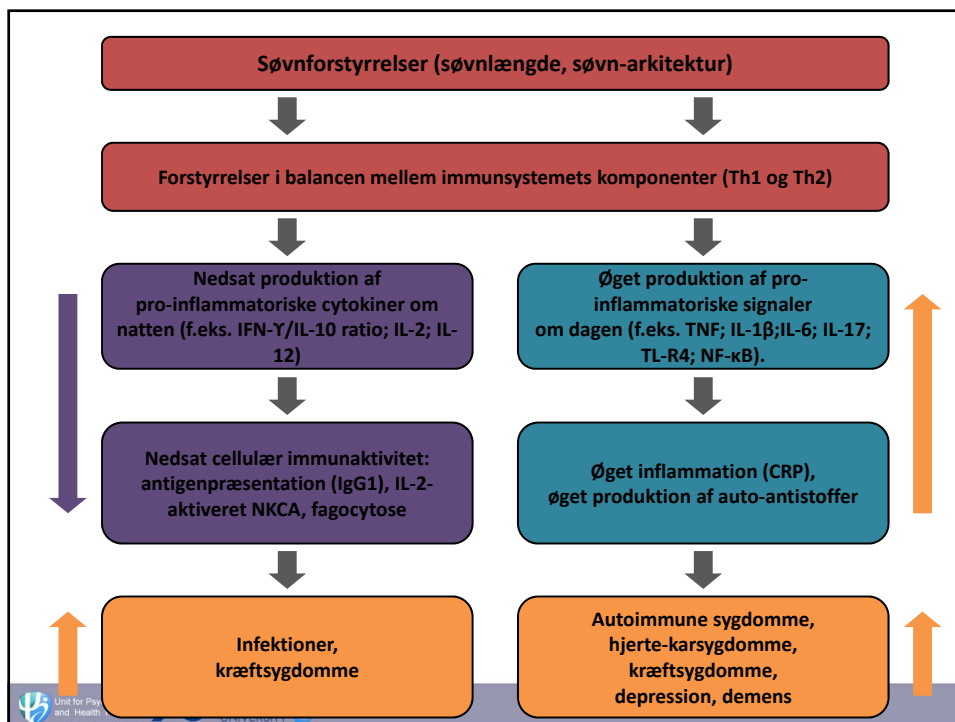
Mulige mekanismer

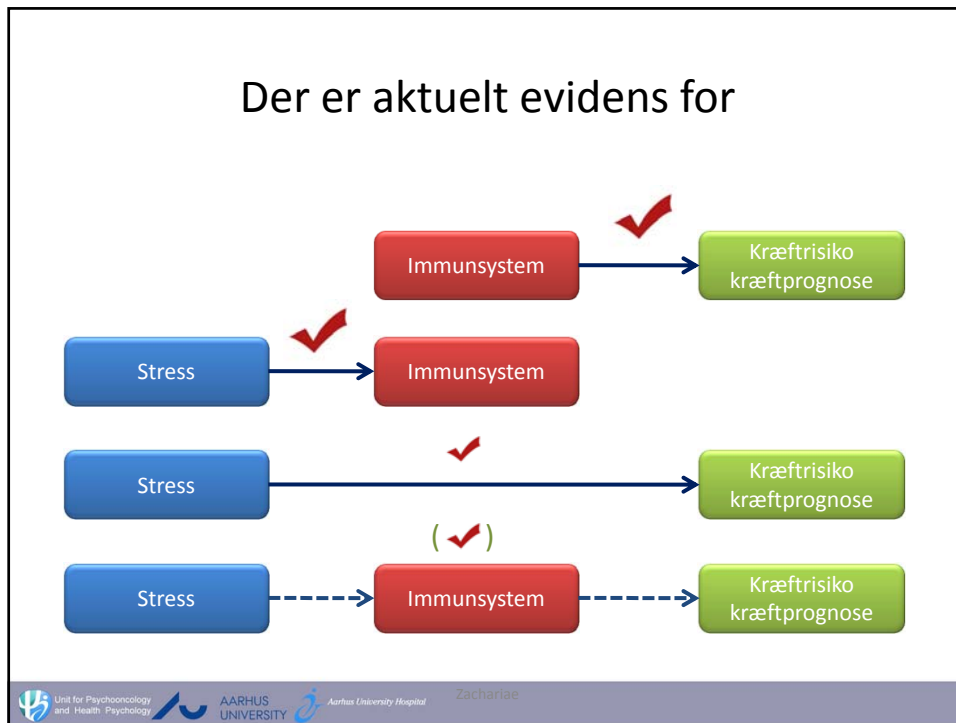
- **Depressive symptomer og søvnforstyrrelser** i malignt melanom og nyrekræftpatienter i IL-2 immunterapi – sammenhænge med **behandlingsrespons** (N= 54)

Kontrolleret for prognostiske markører, var både **depressive symptomer** (OR: 1.2, p = 0.03) og kliniske **søvnproblemer** (PSQI>5) (OR: 4.6; p=0.04) forbundet med **sygdomsprogression**.



Jacobsen D, O'Connor M, Pedersen AF, Bastholt L, Donskov F, Schmidt H, Zachariae R. (abstract)





**PSYKOLOGISK BEHANDLING AF
KRÆFTRELATEREDE
UDFORDRINGER?**

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Stress-reduktion

- Mindfulness-baseret terapi
- Lære nye måder at reagere på overfor fysisk og følelsesmæssigt ubehag med en højere grad af accept og åbenhed
- Meta-analyse af 22 randomiserede, kontrollerede undersøgelser af manualiserede 8-ugers interventioner
- Medium effekt på angst og depression (g=0.37 og 0.44)

The Effect of Mindfulness-Based Therapy on Symptoms of Anxiety and Depression in Adult Cancer Patients and Survivors: A Systematic Review and Meta-Analysis

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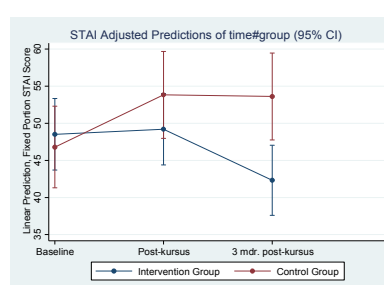
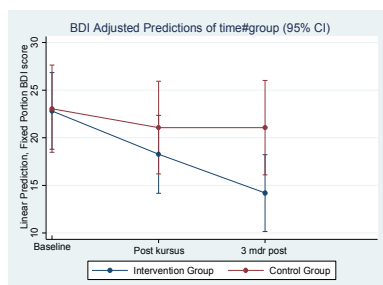
Objective: The use of mindfulness-based therapy (MBT) as a coping strategy has become increasingly popular and research in this field has rapidly expanded. The objective was to review a systematic review and meta-analysis to evaluate the current evidence for the effect of MBT on symptoms of anxiety and depression in adult cancer patients and survivors. Method: Electronic databases were searched and manually screened for relevant studies. Twenty-two independent studies with a total of 1,081 participants were included. Studies were added to quality scores (Q), and overall effect size estimates were performed separately for randomized studies (n = 7), n = 480 and nonrandomized controlled trials (RCTs; n = 601, n = 601). Effect sizes were combined using the random-effects model. Results: In the aggregated sample of randomized trials, average quality score (Q), MBT was associated with significantly reduced symptoms of anxiety and depression from pre- to post-treatment corresponding to medium effect sizes (Hedges's g = 0.40 and 0.42, respectively). The pooled control effect sizes (Hedges's g) of RCTs average quality score: 0.38 and 0.37 for anxiety symptoms (p < .001) and 0.40 for depression (p < .001). These effect sizes remained robust. Furthermore, in RCTs, MBT significantly improved mindfulness skills (Hedges's g = 0.28). Conclusions: While the overall quality of existing clinical trial evidence was moderate, there appear to be some positive evidence from relatively high quality RCTs to support the use of MBT for cancer patients and survivors with symptoms of anxiety and depression.

Keywords: mindfulness, cancer, anxiety, depression, meta-analysis

Anxiety and depression are common and debilitating problems associated with diagnosis and treatment of cancer. Compared to the general population, depression is more prevalent in cancer patients (e.g., Christensen et al., 2009; Hanks & Grunberg, 2006), and depression has been associated with prolonged hospitalization (Fleiss et al., 2002), higher mortality (Duggan & D'Antonio, 2005), and reduced quality of life (Stuck, Linn, & Pruthi-Chavakis, 2006). The devastating effect of depression on health may be largest when depression is comorbid with a medical disease (Moussier et al., 2007). Apparently, there is a bidirectional relationship between cancer and depression. The prevalence of depression increases with severity of cancer, and there is some evidence to suggest that depression predicts cancer progression (Spiegel & Ganz-Davis, 2003). Recent research indicates that depression is associated with various biological markers of inflammation, including so-called pro-inflammatory cytokines (e.g., Houtman, Lam, & de Vries, 2009). Following an infection, the physiological concentrations of pro-inflammatory cytokines have been found to induce symptoms of sickness, including fatigue, sleepiness, loss of appetite, and social withdrawal (Dantzer & Kelley, 2007). From these observations, it has been hypothesized that pro-inflammatory cytokines, due to prolonged activation of the peripheral immune system in some medically ill people, including cancer patients, may act on the brain in ways that lead to the development of symptoms of depression (Dantzer, O'Connor, Fennell, Johnson, & Kelley, 2008).

Lær at tackle ...

- Patientuddannelsesprogrammet "Lær at tackle angst og depression"



849 borgere – heraf 39 med kræft -

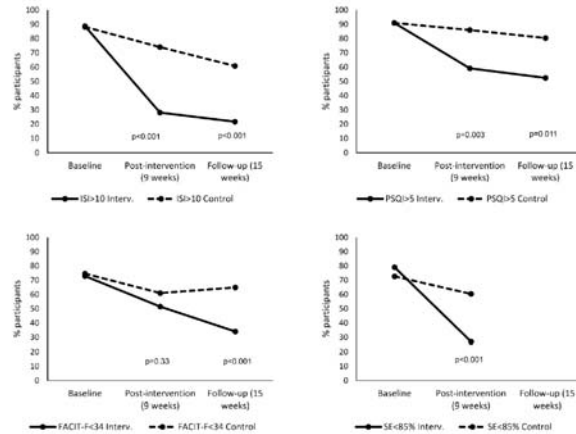
Effekt-mekanisme: forbedret self-efficacy

Christensen S, Jensen AB, Væth M, Zachariae R. Depression and survival in a nationwide cohort of women treated for primary breast cancer. *Psychooncology*, 2016, 25, Suppl. S3, 165.

Internet-delivered CBT-I for insomnia in breast cancer survivors

Changes in proportion of participants with clinically significant impairment (ISI, PSQI, Fatigue, SE)

N=255



Zachariae, et al., J. National Cancer Institute (accepted for publication)



Zachariae

Mindfulness-Based Cognitive Therapy for persistent pain after treatment for primary breast cancer

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Efficacy of Mindfulness-Based Cognitive Therapy on Late Post-Treatment Pain in Women Treated for Primary Breast Cancer: A Randomized Controlled Trial

Mark Sherman, Maya O'Connor, Mia Bote O'Toole, Andrea Breda-Davies, Peter Mann, and Robert Zachariae

ABSTRACT

Purpose: To assess the efficacy of mindfulness-based cognitive therapy (MBCT) for late post-treatment pain in women treated for primary breast cancer.

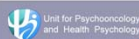
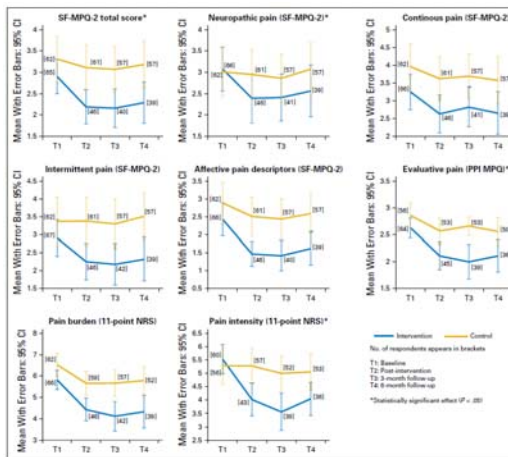
Methods: A randomized trial was conducted that was stratified into 128 women treated for breast cancer requiring breast treatment pain. Women in 2-year post-treatment or post-treatment assessment with 12-point Numeric Rating Scale (NRS) scores indicating ongoing or intermittent breast pain were randomized to MBCT program or a waitlist control group. Pain was the primary outcome and was assessed with the Short Form McGill Pain Questionnaire (SF-MPQ-2), the Present Pain Inventory (PPI), the Pain Coping Questionnaire, and general pain intensity and pain location. Secondary outcomes were quality of life (Health Utilities Index, Health Experiences and Anxiety Scales), and self-reported use of pain medication. All outcome measures were assessed at baseline, post-intervention, and 3-month and 6-month follow-up. Treatment effects were evaluated with mixed linear models.

Results: Statistically significant time × group interactions were found for pain intensity (a 0.81; P = .002), the Present Pain Inventory subscale (a 0.26; P = .008), the SF-MPQ-2 neuropathic pain subscale (a 0.24; P = .038), and SF-MPQ-2 total scores (a 0.23; P = .005). Only pain intensity remained significantly different after correction for multiple comparisons. Statistically significant effects were also observed for quality of life (a 0.02; P = .003) and pain medication use (a 0.02; P = .008). None of the remaining outcomes reached statistical significance.

Conclusion: MBCT showed a statistically significant, robust, and durable effect on pain intensity, indicating that MBCT may be an effective pain-management strategy for women treated for breast cancer. In addition, the effect on neuropathic pain, a pain type identified by women treated for breast cancer, further supports the potential of MBCT for breast cancer survivors.

J Clin Oncol 36:40-48. © 2018 by American Society of Clinical Oncology

INTRODUCTION
Breast cancer (BC) is the most common cancer type among women, with 1.7 million new cases worldwide each year.¹ Although not all cases are curable, patients with BC report high levels of physical and psychological symptoms after treatment,²⁻⁴ underscoring the need for effective rehabilitation programs. However, post-treatment pain is of particular concern because of its high prevalence, with 67% to 79% of women treated for BC experiencing moderate to severe pain for years after surgery.⁵ Although most



Zachariae

Informal caregiving (IC)

- Increased cancer incidence leads to increased caregiver burden
- Caregiver burden:
 - Biopsychosocial reaction to imbalance of care demands relative to personal time, social roles, physical and emotional states, financial and formal resources
- ICs have
 - High levels of distress
 - Poorer physical functioning
 - Poor immune function
 - Increased mortality

Psychology
 Psycho-Oncology (2014)
 Published online in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pon.2144

Review
Cognitive behavioral therapies for informal caregivers of patients with cancer and cancer survivors: a systematic review and meta-analysis

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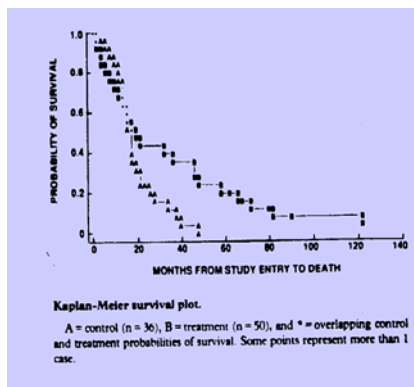
Abstract
 Objective: Informal caregivers (ICs) of patients with cancer and cancer survivors report a number of psychological and physical complaints because of the burden associated with providing care. Given the documented effect of Cognitive Behavioral Therapy (CBT) on ICs' common psychological complaints, such as anxiety and depression, the objective was to conduct a meta-analysis on the effect of CBT for adult ICs.
 Methods: A literature search was conducted in order to identify all literature studies on adult ICs that reported at least one therapeutic component defined as a CBT component.
 Results: Literature searches revealed 36 unique records with sufficient data. These studies were subjected to meta-analysis using random effects models. A small, statistically significant effect of CBT (Hedges' $g = 0.08$, $p = 0.014$) was revealed, which disappeared when randomized controlled trials were excluded alone ($g = 0.04$, $p = 0.20$). A number of variables were explored as moderators. Only the percentage of female participants was positively associated with the effect size.
 Conclusions: Based on the negligible effect of CBT across outcomes, future studies should consider testing traditional CBT methods as these do not appear effective. It is suggested that future interventions orient towards all areas of the biopsychosocial system and control therapies in order to better understand and limit the combined stresses experienced by ICs.
 Received 12 December 2013
 Accepted 11 March 2014
 Accepted 22 March 2014

Meta-analysis of 36 trials (27 RCTs) of CBTs:
 Small overall effect: $g=0.08$, $p= 0.014$
 No effect for RCT's: $g = 0.04$, $p=0.20$
 Moderators:
 Younger age and % women -> larger effects

Alternatives to CBT are needed, e.g., third wave (meta-cognitive) approaches

Psykologisk behandling og kræftprognose

- Før 1989 kun få og dårligt kontrollerede undersøgelser og case-rapporter
- Spiegel et al's undersøgelse publiceret i 1989 gav forhåbninger om at kunne finde virkninger af psykosocial intervention
- Kritiske bemærkninger vedr. Resultaterne (Fox, 1991)



Spiegel et al. 1989.

Psykologisk behandling og kræftprognose

RCT's of psychosocial interventions for cancer patients: effects on survival (1982-2012)

| Author (Year) | Cancer type | N (Intv/ctrl) | Format | Number of sessions (approx.) | Followup (Years) | Result +/- |
|--------------------------|------------------|---------------|------------------|------------------------------|------------------|--------------|
| Linn et al. (1982) | Mixed | 120 (62/58) | Indiv. | ?? | 1 | - |
| Spiegel et al. (1989) | Breast, metast. | 86 (50/36) | Group | 56 | 10 | + |
| Fawzy et al. (1993) | Malign. melanoma | 68 (34/34) | Group | 6 | 5-6 | + |
| Il'yckij et al. (1994) | Mixed | 127 (96/31) | Group | 24 | 11 | - |
| Cunningham et al. (1998) | Breast, metast. | 66 (30/36) | Group | 35 | 5 | - |
| Edelman et al. (1999) | Breast, metast. | 121 (62/59) | Group | 8 | 5 | - |
| Goodwin et al. (2001) | Breast, metast. | 235 (158/77) | Group | ?? | 6 | - |
| Kissane et al. (2004) | Breast, early | 303 (154/149) | Group | 23 | 5 | - |
| Kissane et al. (2007) | Breast, metast. | 227 (147/80) | Group | 56 | 5 | - |
| Küchler et al. (2007) | Gastro-intest. | 271 (136/135) | Indiv. | ?? | 10 | + |
| Spiegel et al. (2007) | Breast, metast. | 125 (64/61) | Group | 56 | 14 | - |
| Boesen et al. (2007) | Malign. melanoma | 258 (128/130) | Group | 6 | 5 | - |
| Andersen et al. (2008) | Breast, regional | 227 (114/113) | Group | 26 | 11 | + |
| Ross et al. (2009) | Colorectal | 249 (125/124) | Indiv. | 10 | 9.5 | - |
| Choi et al. (2012) | Mixed | 237 (118/119) | Indiv. | 10 | 7.5 | - |
| K=15 | Breast: 8 | 2722 | Group: 12 | 6 - 56 | 1 - 14 | +/- 4 |

Take-home-message

- Der er dokumentation for
 - At immunsystemet har relevans for kræftrisiko og prognose
 - At stress kan påvirke immunologiske og inflammatoriske processer af relevans for kræft
 - At stress har betydning for risiko og prognose ved (nogle) kræftformer
 - Lovende, men begrænset dokumentation for direkte mekanismer (f.eks. immunsystemet)

Klinisk

- Omsat til information til patienten
 - Vi kan ikke vide, om stress har været en medvirkende årsag til netop din kræft
 - Vi kan ikke på forhånd vide, om stress vil have indflydelse på netop din prognose
 - Ikke desto mindre: baseret på den aktuelle viden kan det være relevant at fokusere på at tackle de stress-faktorer, der er belaster dig – af hensyn til din livskvalitet, dit sygdoms- og behandlingsforløb og – muligvis – af hensyn til din prognose