



Rigshospitalet

# Depression og andre psykologiske senfølger hos kvinder med brystkræft

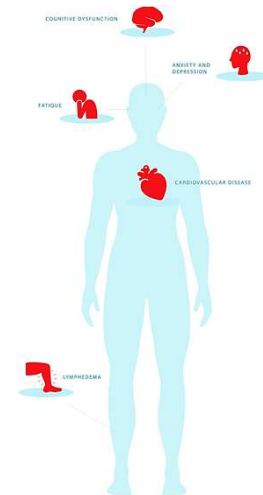
Aarhus Workshop in Breast Surgery  
May 23rd 2019

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**CASTLE - Kræftens Bekæmpelses Nationale Forskningscenter for Senfølger hos Kræftoverlevende**  
Afsnit 9601, Onkologisk Klinik, Center for Kræft og Organsygdomme, Rigshospitalet

## CASTLE

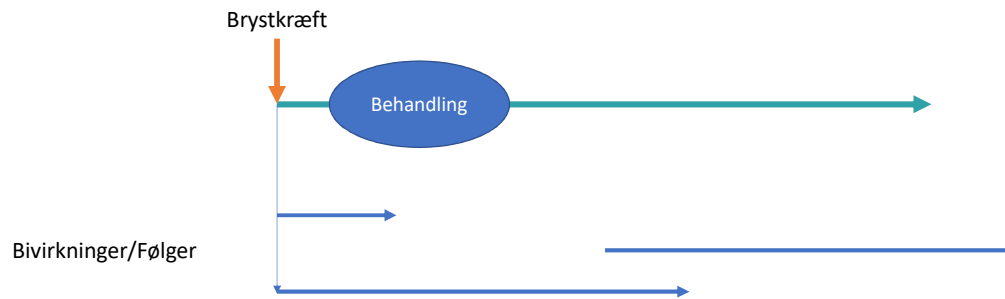
- **CA**ncer Survivorship and **T**reatment **L**ate **E**ffects
- Onkologisk Klinik, Rigshospitalet
- Senfølger der rammer patienter på tværs af kræftdiagnoser
- Særligt fokus:
  - Betydning af **præ-diagnostisk helbred** for senfølger
  - Interventioner til **forebyggelse, tidlig opsporing**
  - **Opfølgingsforløb**
  - Big data



## Senfølger

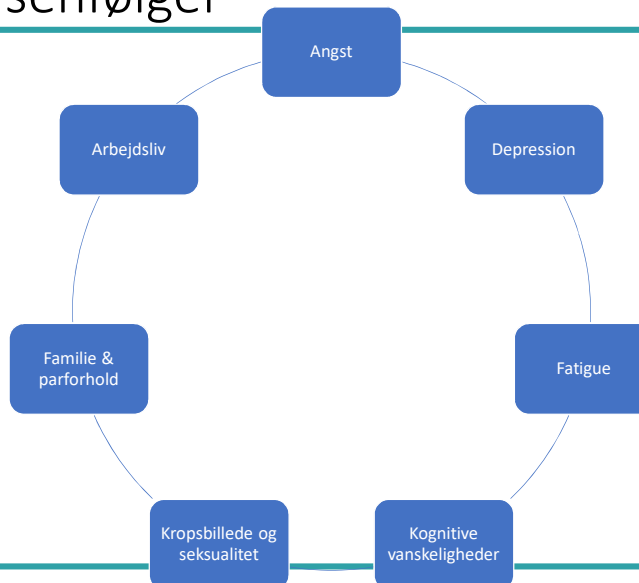
- **Definition**

- Sent opståede følger eller vedvarende



Salz 2015 Eur J Cancer Care, Kjær 2017 Sundhedsstyrelsen

## Psykologiske senfølger



## Psykologiske senfølger - prævalens

- I løbet af 4 uger har 42% haft en psykisk sygdom

- Angsttilstande 17%
- Tilpasningsreaktion 14%
- Depression 9%

Mehnert 2014 JCO

## Depression

- **Kerne symptomer:** forsænket stemningsleje, nedsat lyst/interesse og nedsat energi
- **Risk faktorer:**
  - Familiær disposition, tidlig stress og livsbegivenheder, civil og socioøkonomisk status
  - Personlighed, coping ressourcer
  - Kvinde, østrogen fluktuationer - menopause

Sundhedsstyrelsen 2007, Gordon 2015 Am J Psychiatry

## Konsekvenser af depression

- **Depression kan føre til**
  - Kognitive vanskeligheder
  - Øget risiko for demens
  - Usund livsstil
  - Risiko for non-compliance med medicin
  - Øget risiko for mortalitet
  - 10-14 år kortere forventet levetid
- **Tilbagefald**
  - 60% risiko for ny depressiv episode

Sundhedsstyrelsen 2007, Sin 2016 Ann Behav Med, Grenard 2011 J Gen Intern Med, Laursen 2016 J Affect Disord, Cuijpers 2014 Am J Psychiatry

## Angst

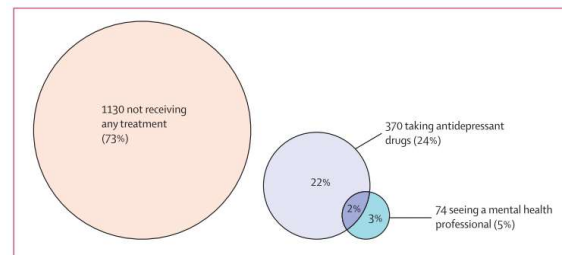
- **Kerne symptomer:** udtalt bekymring, angst, nervøsitet og anspændthed
  - Fobi for noget specifikt
  - Panik angst
  - Generaliseret angst – frit flydende
  - Tilpasningsreaktion

Stark 2000 BJC

## Hvad betyder depression i et kræftforløb?

## Kræft & Depression

- **16 % svær depression** i meta-analyse af 70 studier (10.000 patienter) Mitchell 2011
- **Kun 25 %** af patienter med depression får **behandling** (n=21.000) Walker 2014



**Figure 3: Treatments received by outpatients with cancer and major depression**  
Proportions based on 1538 patients diagnosed with major depression at clinical interview and with complete treatment data. Antidepressant drugs were amitriptyline, citalopram, clomipramine, dosulepin, doxepin, duloxetine, escitalopram, fluoxetine, flupentixol, fluvoxamine, imipramine, lofepramine, mirtazapine, nortriptyline, paroxetine, phenelzine, reboxetine, sertraline, trazodone, trimipramine, venlafaxine.

Walker 2014, Lancet

## Depression & forbrug af sundhedsydelser

- 76% flere besøg (n=5000)  
Mausbach 2017

Mausbach 2017 & 2018 Psychooncology, Mausbach 2018 Health Psychol

## Depression & forbrug af sundhedsydelser

**Table 3.** Multivariate logistic regression model predicting risk for emergency department visit, overnight hospitalization, and 30-day rehospitalization

	ED visit			Hospitalization			30-day re-hospitalization		
	Wald	p-Value	OR (95% CI)	Wald	p-Value	OR (95% CI)	Wald	p-Value	OR (95% CI)
Age	2.62	.105	1.01 (1.00,1.01)	2.57	.109	1.00 (0.99,1.00)	0.00	.991	1.00 (0.99,1.01)
Female	2.54	.111	1.15 (0.97,1.36)	1.41	.236	0.92 (0.80,1.06)	0.66	.416	0.90 (0.69,1.17)
Black	20.64	<.001	2.19 (1.56,3.06)	7.38	.007	1.52 (1.12,2.06)	4.48	.034	1.75 (1.04,2.93)
Hispanic	6.34	.012	1.36 (1.07,1.74)	21.11	<.001	1.57 (1.30,1.91)	1.22	.270	1.22 (0.86,1.72)
Asian	0.75	.387	1.14 (0.85,1.54)	0.03	.863	0.98 (0.77,1.25)	0.38	.538	0.86 (0.52,1.40)
Other race	4.49	.034	0.60 (0.37,0.96)	4.88	.027	0.69 (0.49,0.96)	0.50	.481	1.27 (0.65,2.48)
Medicare	5.00	.025	1.24 (1.03,1.50)	7.38	.007	1.23 (1.06,1.43)	2.92	.087	1.28 (0.97,1.70)
Self-pay	0.29	.592	1.20 (0.62,2.34)	1.94	.163	0.66 (0.37,1.19)	2.28	.131	2.31 (0.78,6.82)
Mths with cancer	11.26	.001	1.19 (1.08,1.32)	8.08	.004	1.12 (1.04,1.22)	3.50	.061	1.16 (0.99,1.36)
Comorbidity index	63.52	<.001	1.32 (1.23,1.41)	74.94	<.001	1.31 (1.23,1.39)	36.43	<.001	1.35 (1.22,1.49)
Metastasis	52.17	<.001	2.10 (1.72,2.57)	130.28	<.001	2.61 (2.22,3.08)	16.07	<.001	1.81 (1.35,2.42)
Depression	65.03	<.001	2.45 (1.97,3.04)	35.60	<.001	1.81 (1.49,2.20)	19.16	<.001	2.03 (1.48,2.79)

Note. OR = Odds ratio. df = 1. Reference group = Male, Caucasian, privately insured, no metastasis, not depressed. Age was centered at 60 years. Months with cancer was centered at 10 months. Comorbidity index was centered at 3.0. Comorbidity index was centered at 3.

Mausbach 2017 & 2018 Psychooncology, Mausbach 2018 Health Psychol

## Depression & forbrug af sundhedsydelser

- 76% flere besøg (n=5000)  
Mausbach 2017
- 113% højere omkostninger  
(n=13.200) Mausbach 2018
- Mere psykologisk behandling >  
færre omkostninger (n=182)  
Mausbach 2018

Mausbach 2017 & 2018 Psychooncology, Mausbach 2018 Health Psychol

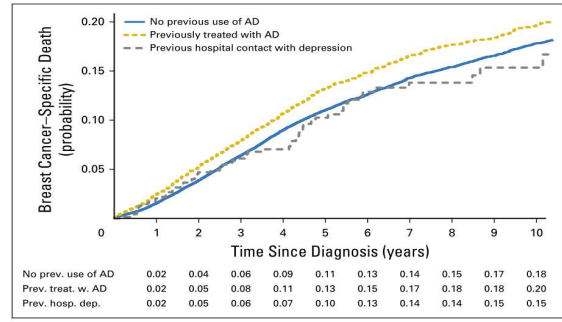
## Depression og brystkræft behandling

- **Adjuverende behandling**
  - Lavere **accept** (51-64%, n=120) Colleoni 2000
  - Lavere **adherence** Lin 2017 (syst.review, n=21), Mausbach 2015 (meta-analysis, n=9)
  - Non-guideline treatment
    - OR 1.14, 1.03-1.27 (n=45.300) Suppli 2017

Colleoni 2000 Lancet, Lin 2017 Breast Cancer Res Treat, Mausbach 2015 Breast Cancer Res Treat, Suppli 2017 JCO

# Depression i behandling for brystkræft

- Kortere **overlevelse** (n=45.300) Suppli 2017
  - Overall (HR 1.11, 1.03-1.20)
  - Brystkræft specific (HR 1.21, 1.14-1.28)

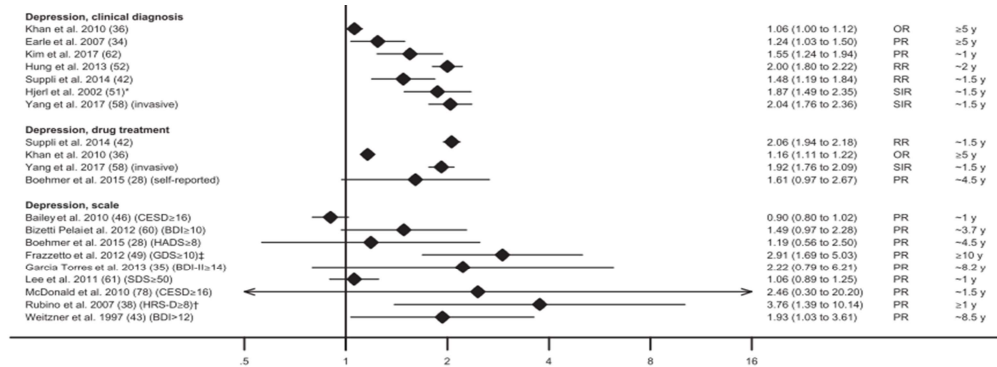


Suppli 2017

Suppli 2017 JCO

# Angst og depression hos kvinder med brystkræft

Øget risiko sammenlignet med baggrundsbefolkning

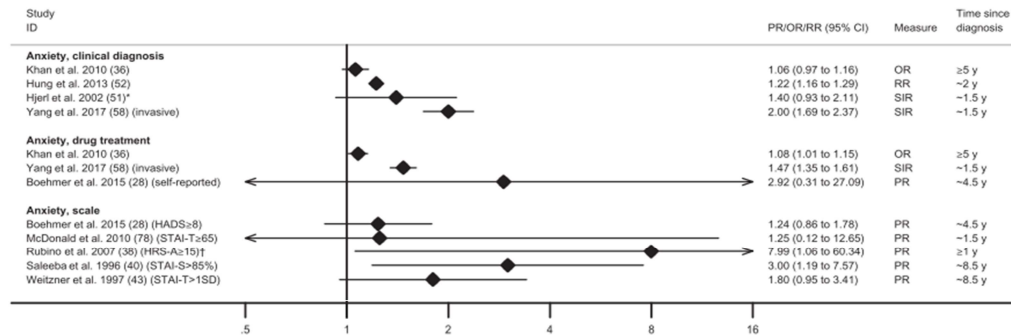


Carreira 2018 JNCI



## Angst og depression hos kvinder med brystkræft

### Øget risiko sammenlignet med baggrundsbefolkning



Carreira 2018 JNCI

## Prævalens af depression under behandling

- **32% depression** på tværs af alle brystkræftpatienter i meta-analyse af 72 studier Pilevarzadeh 2019
- **14% klinisk depression** i meta-analyse af 19 studier Mitchell 2011
- **26% - 45% vedvarende forhøjede symptomer blandt 150-400 patienter** Donovan 2013, Dunn 2013

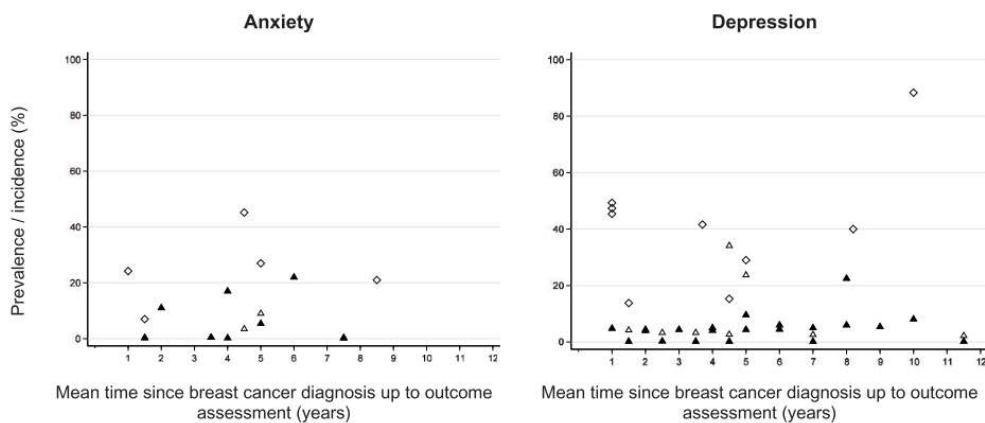
Mitchell 2011 Lancet Oncology, Donovan 2013 Ann Behav Med, Dunn 2011 Health Psychol, Pilevarzadeh 2019 Breast Canc Res Treat

## Hvordan ser det ud på længere sigt?

### 5 og 10 år efter diagnose – kræft generelt

- To kohorter (DE)
- Moderat til svær angst/depression
  - blandt >1000 patienter 5 og 10 år efter diagnose Götze 2015
  - 17% moderat til svær depression
  - 9% moderat til svær angst
- Ingen forskel mellem 5 & 10 år

## Psykologiske senfølger – over tid



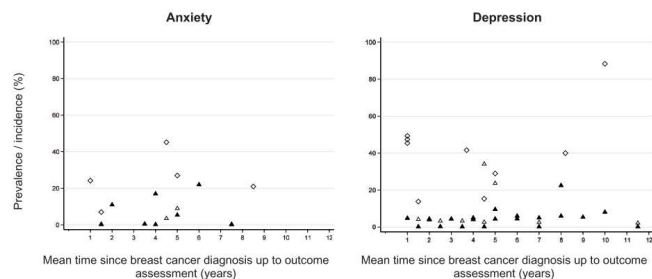
Carreira 2018 JNCI

## Psykologiske senfølger – over tid

### Brystkræftpatienter 1 til 6 år

Maass 2015

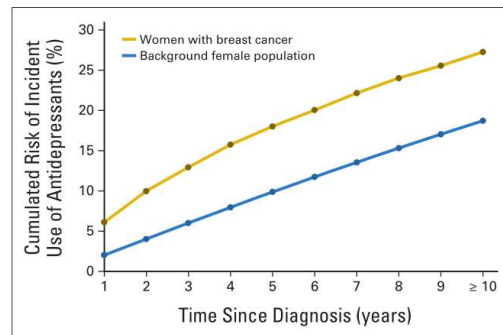
- **Angst 17-33%**
- **Depression 9-66% højere end baggrundsbefolkning – mindre med tiden**



Carreira 2018 JNCI, Maass 2015 Maturitas

## Depression – efter de første år

- **Risiko for brug af antidepressiva øget i 8 år i 44.500 kvinder med og 1.997.700 kvinder uden kræft** Suppli 2015

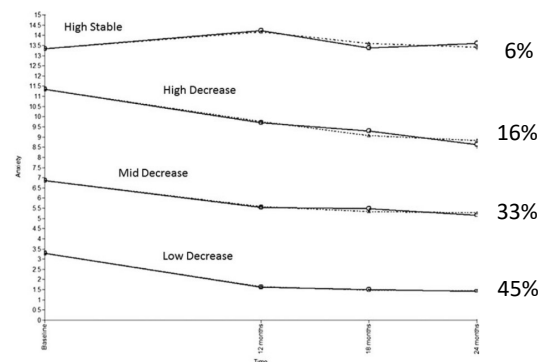


Suppli 2015, JCO

Suppli 2015 JCO

## Forløb efter endt primær behandling

- **Angstsymptomer over 2 år efter diagnose for 725 kvinder** Saboonchi 2015



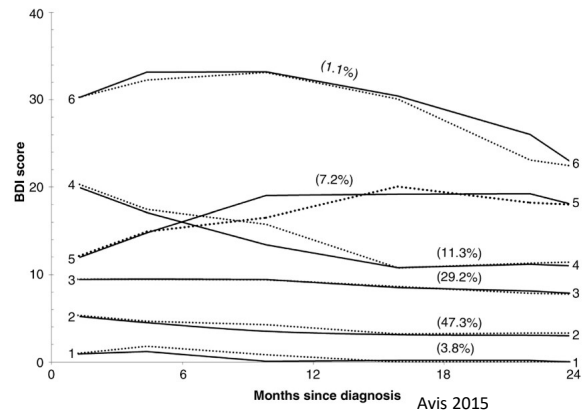
**FIGURE 3** Graphic display of four classes of trajectories of anxiety from baseline to 24 months following first breast cancer surgery. Solid lines denote the sample means and the dotted lines the estimated means based on the selected piecewise latent growth model. The lines for estimated and sample means converge from baseline to 12 months and, thus, cannot be visually distinguished.

Saboonchi 2015

Saboonchi 2015 J Psychosoc Oncol, Burton 2015 Health Psychology, Avis 2015 Cancer Epidemiol Prev Biomarkers

## Forløb efter endt primær behandling

- Angstsymptomer over 2 år efter diagnose for 725 kvinder Saboonchi 2015
- Depressive symptomer over 2 år for 653 kvinder Avis 2015



Saboonchi 2015 J Psychosoc Oncol, Burton 2015 Health Psychology, Avis 2015 Cancer Epidemiol Prev Biomarkers

## Forløb efter endt primær behandling

- Angstsymptomer over 2 år efter diagnose for 725 kvinder Saboonchi 2015
- Depressive symptomer over 2 år for 653 kvinder Avis 2015
- Depressive symptomer blandt 1294 patienter Burton 2015

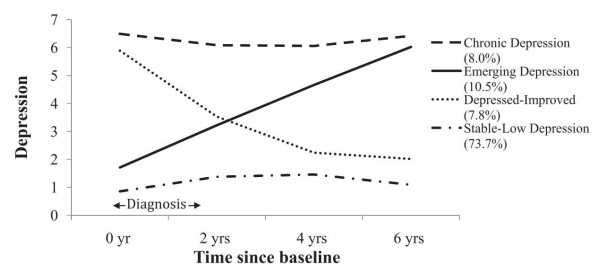


Figure 1. Estimated levels of mean depression score for each trajectory group at each time point within the unconditional model (without covariates),  $n = 1,294$ .

Burton 2015

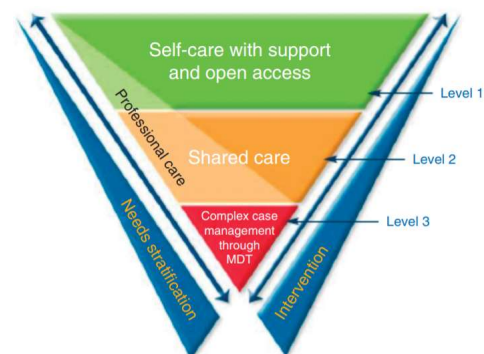
Saboonchi 2015 J Psychosoc Oncol, Burton 2015 Health Psychology, Avis 2015 Cancer Epidemiol Prev Biomarkers

## Opsummering

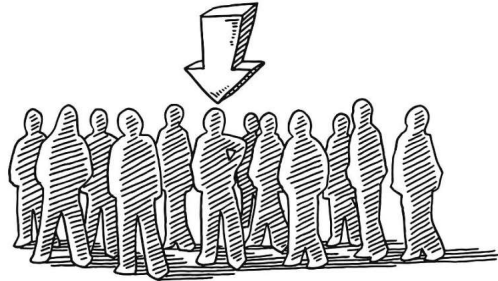
- Omkring 14% af kvinder med brystkræft vil formentlig kunne diagnosticeres med depression i løbet af deres kræftforløb
- Mange flere har høje symptomer
- Symptomerne falder med tiden

## Opfølningsmodel

- Risiko **stratificeret** opfølgning
- Kræver **prædiktiorer**



Men hvem er i risiko?



## Prædiktorer for emotionel distress

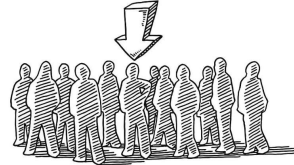
- Review af 39 prospektive studier Cook 2018
  - Alle kræftformer
  - Diagnose > min. 1 år
- Tydelig evidens:
  - Distress ved baseline
  - Neuroticism
- Brystkræft specifikt: Ingen effekt af behandlingstype



Stærkeste prædiktor:  
Baseline distress

## Prædiktorer for psykologisk tilpasning

- Review af 41 prospektive studier Brandao 2017
  - Brystkræft
  - Diagnose > efter diagnose



- Konsistente prædiktorer
  - indkomst
  - fatigue, stadie, fysisk funktion
  - optimisme, trait anxiety, social støtte, coping strategier, baseline psykologisk funktion

Brandao 2017 Psychooncology, Cook 2018 Psychooncology

## Risikofaktorer for angst

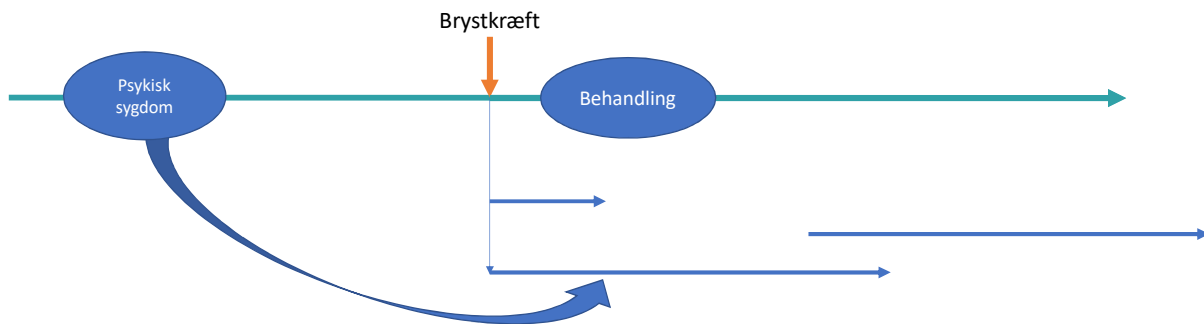
- Risikofaktorer for angst i syv prospektive studier Harris 2017
  - Diagnose > 6-72 mdr
  - God/moderat evidens for:
    - tidligere psykologiske problemer, højere angst/depression ved baseline, yngre alder
  - Kliniske variable prædikterer *ikke* angst

Stærkeste prædiktor:  
tidligere angst/depression

Harris 2017 Psychooncology



## Model



## Prædiktorer for psykologiske senfølger

- Mange prædiktorer undersøges
- Systematiske reviews indeholder studier af varierende follow-up
- De fleste primære studier rapporterer ikke størrelsen af associationen, kontrollerer ikke for baseline symptomer, ser ikke på caseness
- Ingen meta-analyser

## Prædiktionsmodeller

- Modeller der omfatter flere faktorer og samler til én risikoscore
- Der findes meget få prædiktionsmodeller Salz 2015

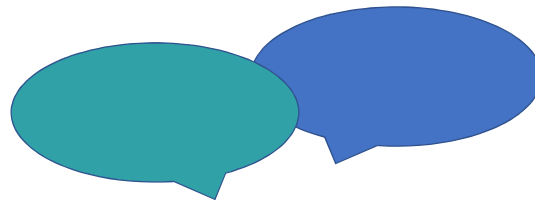
Type of childhood cancer	HODG	NHL	CNS	NEURO	RETINO	BONE	STS	OTHER
S alone	1	1	2	2	2	1	1	1
R alone	3	2	2	2	2	2	2	2
C alone	2	2	2	2	2	2	2	2
S + R	3	2	3	3	3	2	2	2
S + C	2	2	2	2	2	2	2	2
R + C	3	2	3	3	3	3	3	2
S + R + C	3	2	3	3	3	3	3	2

Tidligere & baseline angst/depression

S - surgery; R - Radiotherapy; C - Chemotherapy; HODG- Hodgkin's lymphoma; NHL- Non-Hodgkin's lymphoma; CNS - Central nervous system; NEURO - Neuroblastoma; RETINO- Retinoblastoma; STS - soft tissue sarcoma

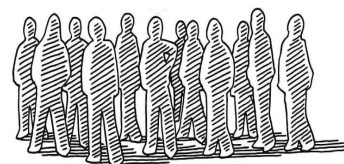
Salz 2015 Eur J Cancer

## Interventioner for depression og distress



## Psykoterapi

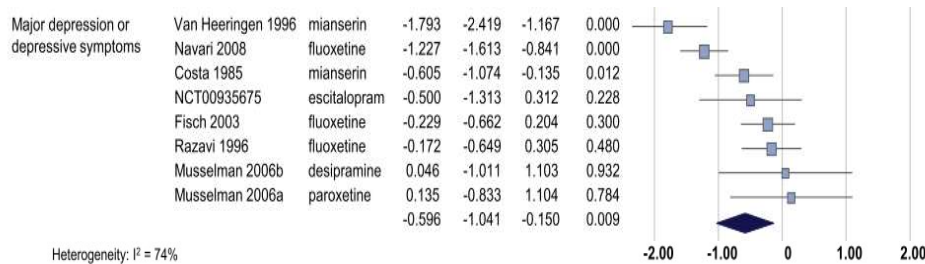
- Meta-analyser: små til store effekter på symptomer på angst og depression
  - Psykoterapi og psykologisk intervention generelt &
  - kognitiv adfærdsterapi for depression
- Ikke fokus på kliniske cases – Interventioner gives til alle
- Ressource intensive
  - 5-20 sessioner ansigt til ansigt Ye 2018



Coutiño-Escamilla 2019 The Breast, Ye 2018 Psychooncology, Matthews 2017 Psychooncology, Jassim 2015 Cochrane Database Syst Rev

## Antidepressiva

- Anbefales til moderat til svær depression i den generelle befolkning
  - Og gentagen depression
- Effekt på depression i meta-analyser hos kræftpatienter



Sundhedsstyrelsen 2007, Ostuzzi 2015 Cancer Treatment Reviews, Riblet 2014 Gen Hospital Psychiatry, Laoutidis 2013 BMC Psychiatry, Hart 2012

# Intervention til høj risiko gruppen?

**Cancer Treatment Reviews**  
journal homepage: [www.elsevierhealth.com/journals/ctrv](http://www.elsevierhealth.com/journals/ctrv)

Hot Topic  
Major depressive disorder in breast cancer: A critical systematic review of pharmacological and psychotherapeutic clinical trials

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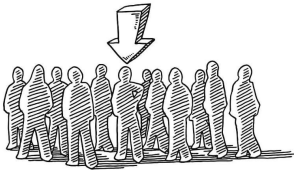
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Antidepressant agents  
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Clinical trials

**ABSTRACT**  
**Background:** While women with breast cancer often face varying levels of psychological distress, there is a subgroup whose symptomatology reaches a threshold for diagnosis of major depressive disorder (MDD). Major depressive disorder is known to influence patient outcomes, such as health-related quality of life and treatment adherence. There are no systematic reviews that evaluate pharmacological and psychotherapeutic treatment trials for MDD among individuals with breast cancer.  
**Methods:** Two authors independently searched MEDLINE, EMBASE, Cochrane and Clinical Trials.gov databases through February 20, 2013 without language restrictions. Core journals, reference lists and citation tracking were also searched. Articles on breast cancer patients were included if they (1) included participants with a diagnosis of MDD; (2) investigated pharmacological or psychotherapeutic treatments for MDD compared to placebo or usual care in a randomized controlled trial (RCT).  
**Results:** Two RCTs on antidepressant treatment met inclusion criteria. However, no RCTs investigating the effects of psychological treatments for MDD in breast cancer were identified. Notwithstanding the paucity of data investigating the effects of psychological treatments for MDD in breast cancer, numerous psychotherapeutic strategies targeting depressive symptoms were identified. Mianserin had significant antidepressant effects when compared to placebo in a 6-week, parallel-group, RCT of Stage I–II breast cancer in women with MDD. Desipramine and paroxetine were reported to be no more efficacious than placebo in a 6-week, RCT of Stage I–IV breast cancer in women with MDD.  
**Conclusion:** The evidence reviewed herein underscores the paucity of data available to guide clinicians in treatment decisions for MDD in individuals with breast cancer. Therefore, the treatment of MDD in breast cancer is primarily based on clinical experience. Some antidepressants (for example, paroxetine) should be avoided in women concurrently taking tamoxifen due to relevant interactions involving the cytochrome CYP2D6.

- Interventioner for klinisk depression/angst Carvalho 2013
- Intervention til patienter med høje, subkliniske scores Matthews 2017



Carvalho 2013 Cancer Treatment Reviews, Matthews 2017 Psychooncology

# Intervention for klinisk depression

- SMART oncology-2 / Depression Care for Patients with Cancer
  - Sygeplejersker, psykiatere, sammen med onkologisk team og egen læge
  - Stor effekt på depression
- Højere omkostning, men 'cost-effective' efter NICE kriterier
- Ingen effekt på overlevelse af depressionsbehandling

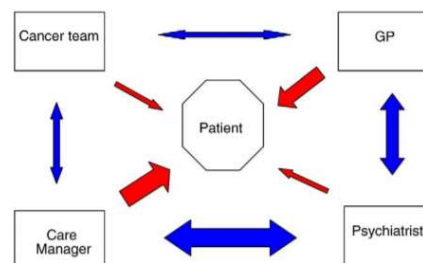
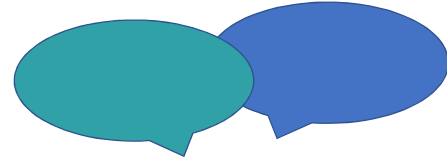


Fig. 1. The collaborative care model in DCPC. Red arrows represent patient contact with health professionals about depression care. Blue arrows represent liaison between health professionals about depression care. N.B. The thickness of the arrows represents the estimated intensity of the contact.

## Intervention for klinisk depression

- Psykoterapeutiske interventioner ved siden af kræftbehandling
  - mindsker depressive symptomer
    - Gruppe kognitiv adfærdsterapi, Interpersonal terapi Qui 2013
  - Øger remission
    - Interpersonel terapi, problemløsningsterapi, korttids støttende terapi Blanco 2019
    - Kort psykodynamisk terap Beutel 2014



Qui 2013 J Psychosom Obstet Gynecol, Blanco 2019 Breast Canc Res Treat, Beutel 2014 Ann Oncol

## Hvad vi ikke ved

- Prædiktionsmodel for angst og depression?
- Forebyggende interventioner?
- Effekt på klinisk angst og depression?

\*\*\*

## Take home



- Depression har store konsekvenser for behandlingsforløbet
- Der findes effektiv behandling for nuværende depression hos kræftpatienter
- Tidligere depression prædikterer depression som senfølge

## RCT: kan antidepressiva forebygge depression?

- Kvinder med brystkræft og
  - tidligere depression eller familiær disposition
  - Nuværende depression
- Randomiseres til placebo eller sertralin
- 12 måneder

Tak for opmærksomheden!

*Kontakt: [annika.von.heyman@regionh.dk](mailto:annika.von.heyman@regionh.dk)*