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Faculty of Health and Medical Sciences

### Tung styrketræning hos kvinder i adjuverende kemoterapi for brystkræft og risiko for udvikling af lymfødem

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UCSF ORE A center established and supported by The Danish Cancer Society and The Novo Nordisk Foundation Rigshospitalet

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### "Risk reduction" anbefalinger



- Undgå tunge løft
- Undgå fysisk krævende aktiviteter med armene

**= Undgå styrketræning**

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### Abreast in a Boat- a race against breast cancer



McKenzie D, CMAJ 1998;159:376-8

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## Konsistent evidens

Journal of Physiotherapy 93(2013) 10-16

**Journal of PHYSIOTHERAPY**  
 Elsevier  
 Research  
 Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review  
 Vincent Singh Paramasundari<sup>1</sup>, Dave Roberts<sup>2</sup>  
<sup>1</sup>Physiotherapy Department, The General Hospital, Leeds; <sup>2</sup>Faculty of Health and Life Sciences, DePaul University, United Kingdom

**Abstract**  
 The purpose of this study was to assess the safety and efficacy of progressive resistance training (PRT) in breast cancer. A systematic review and meta-analysis published in November 2013 was reproduced in the effect of PRT on lymphoedema. **Keywords:** breast cancer, lymphoedema, weight training, progressive resistance training, systematic review, meta-analysis.

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 breast cancer, lymphoedema, weight training, progressive resistance training, systematic review, meta-analysis.

**Background:**  
 Breast cancer is the most common cancer among women worldwide. Lymphoedema is a common complication of breast cancer, affecting up to 10% of women. It is characterized by swelling of the arm and/or breast, which can be painful and affect quality of life. Weight training (WT) is a form of exercise that involves using resistance to build muscle strength and endurance. It is a safe and effective way to improve physical fitness and reduce the risk of chronic diseases. However, there is concern that WT may exacerbate lymphoedema in women with breast cancer. This systematic review and meta-analysis aimed to assess the safety and efficacy of PRT in breast cancer-related lymphoedema.

**Methods:**  
 A systematic search of the literature was conducted using the following keywords: 'breast cancer', 'lymphoedema', 'weight training', 'progressive resistance training', 'systematic review', 'meta-analysis'. The search was limited to English-language articles published between 1990 and 2013. The search was conducted in the following databases: Medline, Embase, CINAHL, and Cochrane Database of Systematic Reviews. The search was limited to English-language articles published between 1990 and 2013. The search was conducted in the following databases: Medline, Embase, CINAHL, and Cochrane Database of Systematic Reviews.

**Results:**  
 The search identified 10 studies that met the inclusion criteria. The studies included a total of 100 women with breast cancer-related lymphoedema. The studies were conducted between 1990 and 2013. The studies included a total of 100 women with breast cancer-related lymphoedema. The studies were conducted between 1990 and 2013.

**Conclusion:**  
 The results of this systematic review and meta-analysis suggest that PRT is safe and effective for women with breast cancer-related lymphoedema. PRT does not appear to exacerbate lymphoedema and may actually improve lymphoedema symptoms. PRT is a safe and effective way to improve physical fitness and reduce the risk of chronic diseases in women with breast cancer-related lymphoedema.

**References:**  
 1. Singh Paramasundari V, Roberts D. Weight training is not harmful for women with breast cancer-related lymphoedema: a systematic review. *Journal of Physiotherapy*. 2013;93(2):10-16.

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## Styrketrænings dosering



Meget tung 1-5 RM  
 Tung 5-8 RM  
**Mod. tung 8-12 RM**  
 Moderat 10-15 RM  
 Let 15-20 RM

1 Repetition Maximum (1RM) = 100%  
 Estimeret repetitioner ved percent af 1RM

Reps.	1	2	3	4	5	6	7	8	9	10	12	15
% 1RM	100	95	93	90	87	85	83	80	77	75	67	66

Baechle TR, Earle RW, Wathen D 2000

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## Hvorfor tung styrketræning?

<b>Gevinst ved styrketræning</b>	<b>Sequelae fra brystkræft og behandling</b>
Øger knogle densitet	I risiko for udvikling af osteoporose
Øger muskelmasse	Sarkopeni, metaboliske syndrom
Øger vitalitet	Træthed
Øget muskelstyrke	Muskel svaghed
Forbedret "body image"	Negativ kropspfattelse
Forebygge muskuloskeletale skader	Lymfødem?

**Potentiel ekstra gevinst med styrketræning med tunge vægte grundet dosis-respons forhold**

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## Formålet med Phd afhandlingen

At undersøge hvor vidt det er sikkert at styrketræne med tung belastning hos brystkræft opereret der er i risiko for at udvikle brystkræftrelateret lymfødem under adjuverende kemoterapi.



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## Afhandlingen består af 3 studier / 4 artikler

**Study 1 / Paper I**  
Bloomquist K, Karlsmark T, Christensen KB, Adamsen L. Heavy resistance training and lymphedema: Prevalence of breast cancer-related lymphedema in participants of an exercise intervention utilizing heavy load resistance training. *Acta Oncol.* 2014;53(2):215-25

**Study 2 / Paper II**  
Bloomquist K, Hayes S, Adamsen L, Møller T, Christensen KB, Ejlersten B, Oturai P. A randomized cross-over trial to detect differences in arm volume after low- and heavy-load resistance exercise among patients receiving adjuvant chemotherapy for breast cancer at risk for arm lymphedema: study protocol. *BMC Cancer.* 2016;16:517

**Study 2 / Paper III**  
Bloomquist K, Oturai P, Steele M, Adamsen L, Møller T, Christensen KB, Ejlersten B, Hayes S. Heavy-load lifting: Acute response in breast cancer survivors at risk for lymphedema. *Med Sci Sports Exerc.* 2018;50(2):187-95

**Study 3 / Paper IV**  
Bloomquist K, Adamsen L, Hayes S, Lillelund C, Andersen C, Christensen KB, Oturai P, Ejlersten B, Tuxen MK, Møller T. Heavy-load resistance exercise in pre-diagnosis physically inactive women at risk of breast cancer-related lymphedema during adjuvant chemotherapy: a randomized trial. Manuscript prepared for submission to *Acta Oncologica.*



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## Studie 2

BMC Cancer


**STUDY PROTOCOL** Open Access

**Heavy-Load Lifting: Acute Response in Breast Cancer Survivors at Risk for Lymphedema**

**Formål**  
At vurdere den umiddelbar respons af ekstracellulær væske i armene efter styrketræning med let- sammenlignet med tung belastning hos brystkræft opereret i risiko for at udvikle arm lymfødem.

**Hypotese**  
At den akutte respons vil være ens mellem de to vægt belastninger (equivalent).

**Abstract**  
Breast cancer-related lymphedema is a common complication for women with breast cancer. Heavy resistance training (HRT) is a well-established exercise intervention for breast cancer survivors, regularly affecting both function and quality of life. However, the prevalence of lymphedema in breast cancer survivors is high, and the impact of HRT on lymphedema is unclear. The aim of this study is to evaluate the acute response of arm volume to HRT in breast cancer survivors at risk for lymphedema. The study is a randomized, crossover trial comparing two HRT protocols: a light load protocol (10 kg) and a heavy load protocol (20 kg). The primary outcome is the change in arm volume (ALV) measured by water displacement. Secondary outcomes include changes in arm circumference, skin temperature, and heart rate. The study is registered at ClinicalTrials.gov (NCT02701212) and BMC Cancer (2016:16:517).



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## Design og metode

Randomiseret cross-over studie

- Alle deltog i styrketræning med 4 øvelser for arme/overkrop
  - Let (2 sæt af 15-20 RM)
  - Tung (3 sæt af 5-8 RM)
- En uge i mellem

Rekruttering

- Krop og Kræft database
- Center for Kræft og Sundhed

Randomiseret rækkefølge (let- eller tung styrketræning først)

Bloomquist et al., 2018

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## Deltagelses kriterier

<p>Inklusions kriterier</p> <ul style="list-style-type: none"> <li>• Modtagelse af standard adjuverende kemoterapi for stadie I-III brystkræft</li> <li>• Unilateral brystkirurgi og aksil dissektion</li> <li>• Ingen tidligere brystkræft</li> </ul>	<p>Eksklusions kriterier</p> <ul style="list-style-type: none"> <li>• Prævalent lymfødem</li> <li>• Forhindringer til styrketræning</li> <li>• Deltagelse i tung styrketræning (&gt;1 /ugen) indenfor den sidste måned</li> </ul>
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## Målemetoder / Effektmål

Tre målemetoder

- Bioimpedans Spektroskopi (BIS) / Ekstracellulær væske (primær)
- Dual x-ray absorptiometry (DXA) / % forskel volumen mellem armene
- Numeric Rating scale (NRS) / lymfødem symptomer i armene

**Målt umiddelbart før, efter samt 24 and 72 timer efter træning**

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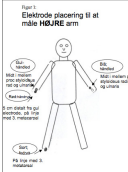
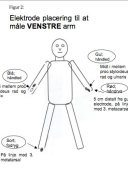
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## BIS

BIOMPEDANCE SPECTROSCOPY (BIS)

- Nem og hurtig direkte måling af ekstracellulær væske
- Impedans (modstand) måling: mere væske = mindre modstand
- Høj sensitivitet til at måle en begyndende lymfødeme
- L-Dex score
  - Tager højde for arm dominance
  - Valideret cut-off

Cornish 1999, Ward 2011, Czerniec 2010

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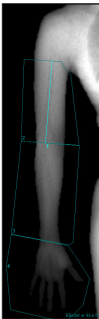
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## DXA (separate arm scans)

Densitet til volumen omregning

- Fedt (0.9 g/ml)
- Muskel masse (1.1 g/ml)
- Knogle mineral indhold (1.85 g/ml)

Measure 1	BMC	Fedt	Muskel	Væv	ml
Højre overarm	47,7	408	553	961	981.8443988
Højre underarm	50,4	183	487	670	673.3038493
Højre hånd	28,1	61	190	251	255.6942397
Højre arm	128,2	652	1230	1882	1910.842479
Venstre overarm	48	444	599	1043	1063.624734
Venstre underarm	43,8	156	491	647	643.3726454
Venstre hånd	23,6	65	185	250	253.1607972
Venstre arm	115,4	665	1275	1940	1960.358176



Inter-arm volume % forskel =  $\frac{\text{at-risk arm} - \text{unaffected arm}}{\text{at-risk arm}} \times 100$

Gjorup et al., 2010

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## NRS (0-10 skala)

- Selv-rapporteret symptomer (ingen gener til værst-tænkelig)
- Fire symptomer
  - Tyngde
  - Spænding
  - Smerte
  - Hævelse

Hawker 2011, Cormie 2013

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### Resultater Studie 2

- Varieret individuel respons- ingen entydig tendenser



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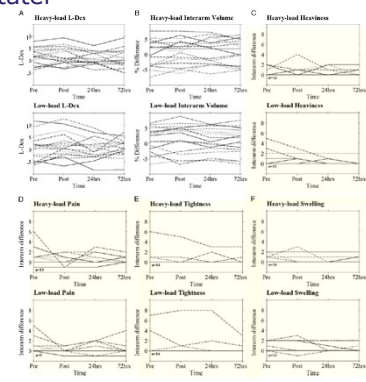
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### Resultater



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### Resultater Studie 2

- Varieret individuel respons- ingen entydig tendenser
- Den umiddelbar respons til styrketræning med let og tung styrketræning var det samme- med undtagelse af ekstracellulær væske ved 72 timer post træning som indikerede mindre væske efter tung vægtbelastning



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### Main findings

TABLE 4. Equivalence between resistance exercise intensities for all outcomes (n = 17).

	Estimated Mean Difference <sup>a</sup>	Equivalence 90% CI
L-Dex ( $\pm 3.0$ ) <sup>b</sup>		
Postexercise	-0.97	-2.09 to 0.16
24 h postexercise	-0.14	-1.63 to 1.35
72 h postexercise	-1.00	-3.17 to 1.17
Interarm volume % difference ( $\pm 3.0$ ) <sup>b</sup>		
Postexercise	0.21	-0.89 to 1.31
24 h Postexercise	1.09	0.41 to 1.78
72 h Postexercise	0.96	-0.09 to 2.02
Interarm difference for pain ( $\pm 1.0$ ) <sup>b</sup>		
Postexercise	0	-0.43 to 0.43
24 h postexercise	-0.06	-0.58 to 0.46
72 h postexercise	-0.06	-0.61 to 0.49
Interarm difference for heaviness ( $\pm 1.0$ ) <sup>b</sup>		
Postexercise	0.24	-0.23 to 0.70
24 h postexercise	0.18	-0.32 to 0.67
72 h postexercise	0.24	-0.38 to 0.85
Interarm difference for tightness ( $\pm 1.0$ ) <sup>b</sup>		
Postexercise	-0.06	-0.45 to 0.34
24 h postexercise	-0.11	-0.50 to 0.27
72 h postexercise	0.20	-0.37 to 0.77
Interarm difference for swelling ( $\pm 1.0$ ) <sup>b</sup>		
Postexercise	0	-0.33 to 0.33
24 h postexercise	0	-0.33 to 0.33
72 h postexercise	0.06	-0.42 to 0.54

<sup>a</sup>Boilance indicates that equivalence was not demonstrated.  
<sup>b</sup>Equivalence margin.  
<sup>c</sup>Estimated mean difference calculated using a GEE model with heavy load as comparator (heavy minus low).



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### Conclusion

- Fandt ingen evidens som indikerede at man burde undgå tunge løft.
- Skal bekræftes med gentagne styrketræningssessioner med tunge belastninger



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### Studie 3 (i review)

Formål

Vurder effekten af 12 ugers :

- Superviseret, multimodal intervention, **inkluderede tung styrketræning** (HIGH)
- Hjemme baseret gang intervention (LOW)

Hypotese:  
 Lymfødem: sammenlignelig effekt mellem grupperne (equivalent)  
 Muskel styrke: HIGH stærkere  
 Fysisk funktion: HIGH bedre



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## Rekruttering og kriterier


January 2014-July 2016; Onkologisk afd. Herlev Hospital og Rigshospitalet

**Inklusion**

- Adjuvant kemoterapi (stadie I-III brystkræft)
- WHO performance status of 0-1
- **Præ-diagnose fysisk inaktiv**; < danske nationale anbefalinger
  - Screenet af onkolog eller sygeplejerske ved første møde
  - 150 minutter moderat aerob aktivitet
  - 2 x 20 min høj-intens aerob aktivitet

**Eksklusion**

- Diagnosticeret akut koronar hjerte syndrome indenfor sidste 6 måneder
- Symptomatisk hjerte sygdom
- Patologisk ekkokardiogram
- Kontraindikation for træning beskrevet i journal
- Ikke kan læse eller forstå dansk



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## Design / Intervention

**HIGH intervention**


Monday	Tuesday	Wednesday	Thursday	Friday
<b>Part I: Body &amp; Cancer</b> 6 weeks, 9 h/week				
Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h) Swedish massage (0.5 h)	Body awareness (1.5 h) Relaxation (0.5 h)	Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h)	Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h)	Aerobic and resistance exercise (1.5 h) Relaxation (0.5 h) Swedish massage (0.5 h)
<b>Part II: 'All-sport'</b> 6 weeks, 6 h/week				
Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)		Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)		Aerobic and resistance exercise and e.g. ballgames, dancing (2 h)

**LOW intervention**

Week 1	Week 2	Week 4	Week 6	Week 9	Week 12
Pedometer consultation	Pedometer consultation	Pedometer consultation	Pedometer consultation	Pedometer consultation	Pedometer consultation

**Both interventions**

Baseline	Week 6	Week 12	Week 39
Health promotion counselling	Health promotion counselling	Health promotion counselling	Health promotion counselling



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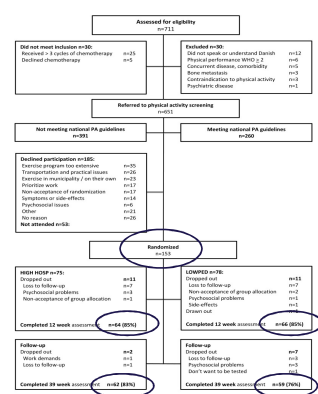
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**Assessed for eligibility** n=711

- Did not meet inclusion n=60
- Reached 11 cycles of chemotherapy n=25
- Declined chemotherapy n=35
- Failed to meet n=6
- Did not know or understand Danish n=2
- Physical performance WHO 2 n=6
- Concurrent disease, comorbidity n=5
- Some medication n=3
- Substitution for physical activity n=1
- Psychiatric disease n=1

**Referred to physical activity screening** n=651

- Not meeting national PA guidelines n=303
- Meeting national PA guidelines n=348

**Randomised** n=348


- Declined participation n=86
- Declined program too extensive n=5
- Transportation and practical issues n=32
- Exercise in municipality / on their own n=25
- Practical issues n=17
- Non-acceptance of randomisation n=17
- Reluctance or side-effects n=4
- Psychological issues n=1
- Other n=2
- Not shown n=3
- Not attended n=12

**HIGH n=171**

- Disrupted trial n=1
- Lost to follow-up n=1
- Psychological problems n=1
- Non-acceptance of group allocation n=1
- Completed 12 week assessment n=64 (37%)
- Completed 39 week assessment n=42 (25%)

**LOW n=177**

- Disrupted trial n=2
- Lost to follow-up n=2
- Non-acceptance of group allocation n=2
- Psychological problems n=2
- Substitution for physical activity n=1
- Other lost n=1
- Completed 12 week assessment n=62 (35%)
- Completed 39 week assessment n=39 (22%)



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## Effektmål

Randomiseret parallel gruppe studie; sekundære effektmål


Lymfødem

- Ekstracellulær væske (BIS)
- % forskel volume i mellem armene (DXA helkrop skan)
- Symptomer (NRS)\*
- Selv-rapporteret hævelse (struktureret interview)\*

Muskelstyrke i armene (1 RM chest press)\*

Brystkræft specifik symptomer og funktion (EORTC-BR23)\*

**Målt ved baseline, 12 og 39 uger post-intervention \*og efter 6 uger**



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## Resultater Studie 3

- Ingen forskel mellem grupperne efter 12 uger hvad angår hævelse målt ved BIS og selv-rapporteret symptomer (tyngde, stramning, hævelse).
- Større reduktioner af smerter og arm volume I HIGH gruppen ved 12 uger.
- Øget muskelstyrke I HIGH gruppen sammenlignet med LOW gruppen (P <0.05, 3 kg (1-5 kg 95% CI)).
- Klinisk relevant reduktioner af bryst og arm symptomer i HIGH gruppen. (Ikke signifikant forskel mellem grupperne).



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## Konklusion

Resultaterne fra afhandlingen indikere at kvinder opereret for brystkræft i risiko for at udvikle arm lymfødem kan:

- deltage i og -
- profitere af

superviseret tung styrketræning under behandling med taxan-baseret kemoterapi uden øget risiko for udvikling af lymfødem.



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### Hvad bidrager afhandlingen med?

- Udfordrer traditionelle anbefalinger om at undgå tunge løft
- Støtter paradigmeskift:
  - Systematisk patient undervisning- viden om symptomer (f. eks tyngde, spændingsfornemmelse, hævelse, snurren, prikken)
  - Anbefalinger i højere grad baseres på den enkeltes livstids risiko for lymfødem **udfra kendte risiko faktorer**
  - Opfordres og støttes til vægt tab eller vedligeholdelse af normal vægt
  - Opfordres og støttes til fysisk aktivitet - start lavt og bygge op- og altid med hensyntagen til evt. symptomer
  - Vedvarende symptomer på den opereret side skal udløse vurdering hos en lymfødemterapeut

American Society of Breast Surgeons, 2017

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### Lymphema Stadieinddeling

**Stadie 0 Subklinisk stadium, hvor hævelsen ikke er synlig til trods for en nedsat transportkapacitet. Dette stadium kan vare fra måneder til år før hævelsen bliver synlig. Reversibel.**

**Tidlig intervensering = bedre lymfødem prognose**

Stadie 1 Der ses pitting ødem som forsvinder ved elevation af ekstremiteterne.

Stadie 2a/b Elevation alene reducerer sjældent hævelsen. Der kan være både pitting og non-pitting ødem.

Stadie 3 Vævet er hårdt (fibrotisk) og pitting er ikke muligt. Huden ses fortykket og furet med hyperpigmentering og vortelignende forandringer.

International Society of Lymphedema, 2016

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### "Risk reduction" anbefalinger



- Flyve med kompressionsærme
- Undgå ekstrem temperatur
- Undgå blodprøvetagning på opereret side
- Undgå blodtryksmåling på opereret side
- Undgå hud infektioner

Asdourian et al., 2016

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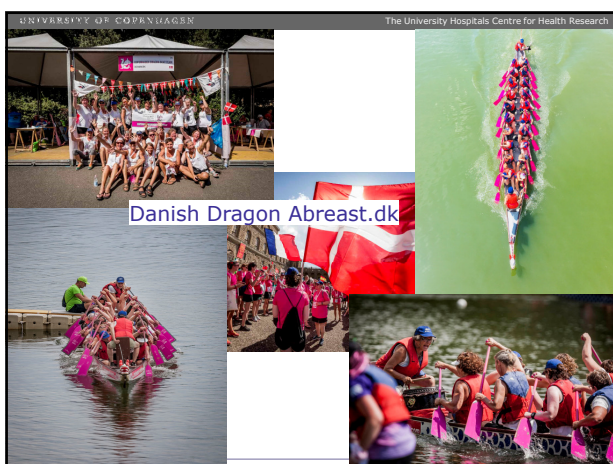
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