Physical training as a way to reduce the burden from late effects, - a review of the literature.

#### Aarhus Breast Surgery Workshop 2022

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# About breast cancer

- The most prevalent cancer among women
- Each year about 4500 women are diagnosed with breast cancer in DK
- The survival rate have been increasing over the last decades
- Today more then 70.000 women are living after a breast cancer diagnosis in DK



# Improved and increased treatment

| • Surgery,                              | 100% |
|---|------|
| <ul> <li>Radiotherapy,</li> </ul>       | 80%  |
| <ul> <li>Chemotherapy,</li> </ul>       | 40%  |
| <ul> <li>Endocrine therapy,</li> </ul>  | 80%  |
| <ul> <li>Antibody treatment,</li> </ul> | 20%  |
| <ul> <li>Immune therapy,</li> </ul>     | -    |
| • Bisphosphonate treatment,             | 60%  |





### Late effects after a breast cancer diagnose

General late effects after cancer and cancer treatment

Specific locoregional late effects Late effects after the specific systemic treatment

Treatment induces secondary diseases



Δ

# Physical activity as an intervention

- Studies in healthy (and elderly) populations have shown:
  - Improved cognitive function
  - Decrease the risk of developing osteoporosis
  - Seem so slow down the progression of dementia
  - A cornerstone in cardiac rehabilitation





# What is physical activity ?

- Resistance training
- Aerobic training
- Specific training elements
- Rigorous activity



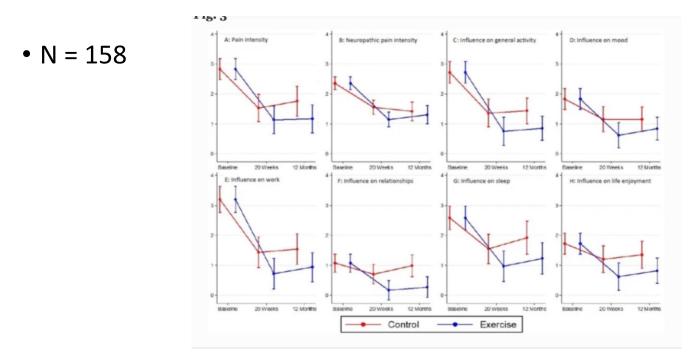
## Relevant late effects for physical interventions

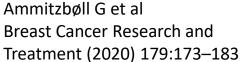
- Arm and shoulder morbidity
- Lymph eodema
- Fatigue
- Cognitive impairment
- Poly-neuropathy



## Persistent pain and physical activity

• A randomised study of the effect of resistence training on "post surgery" pain







# Physical training and menopausal symptoms

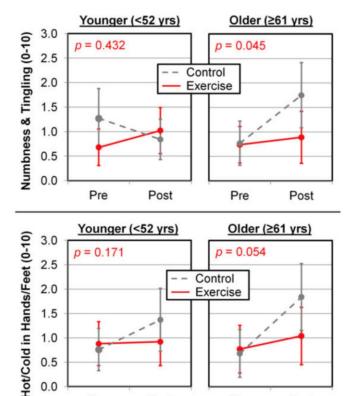
- Randomised study of a combined intervention:
  - Cognitive behavioural therapy (CBT) and physical exercise
- N = 422
- Results:
  - Positive effects on the perceived burden of hot flashes and night sweats (as assessed by the Hot Flush Rating Scale)
  - and on the level of sexual activity (a positive effect) were observed only in the groups that underwent CBT.



Duijts SFA et al *J Clin Onco, 2012 30:4124-4133.* 

# Physical activity and poly-neuropathy

- A randomised study of 355 cancer patients (79% breast cancer ptt)
- Intervention: a 6 weeks home based exercise program (walking and resistance exercise)



Post

Klaerkner IR et al Support Care Cancer. 2018 April; 26(4): 1019–1028



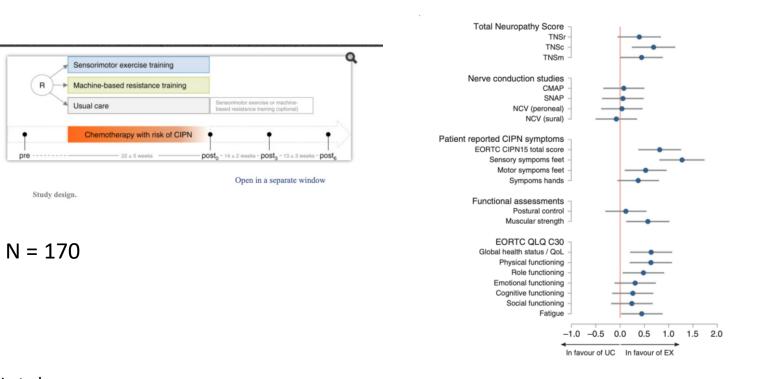
Post

Pre

0.0

Pre

## Physical activity and poly-neuropathy





Müller J et al British Journal of Cancer (2021) 125:955–965

## Physical activity and poly-neuropathy - a focused intervention

- A randomized study evaluating a specific intervention aiming at strengthen balance and postural stability.
- N= 36 breast cancer patients treated with paclitaxel
- Results showed a significant improvement in postural stability, but no impact upon general well-being or Quality of life

Vollmers PL et al Journal of Cancer Research and Clinical Oncology (2018) 144:1785–92



# Physical training and fatigue

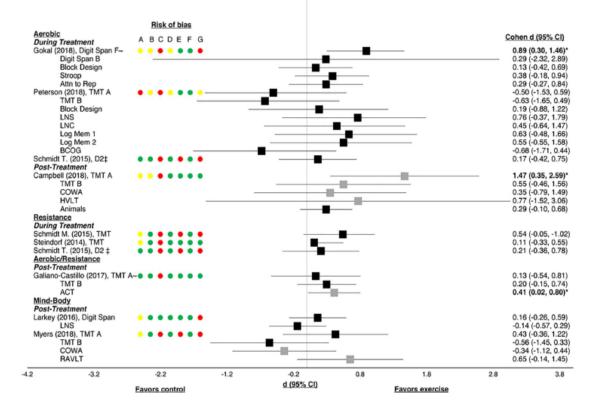
- 20 studies included, with a total of 1783 women
- Different interventions
- Results:
  - supervised resistance training and supervised intervention of combined resistance and aerobic training are the most effective in reducing fatigue, especially for women undergoing chemotherapy

Medeiros Torres D et al Supportive Care in Cancer (2022) 30:4651–4662



#### Physical training and cognitive problems

#### - a meta analysis of 29 trials



Cambell KL et al: Phys Ther 2020 Mar 10;100(3):523-542. The authors conclusion:

"More high-quality and appropriately powered randomized controlled trials designed to specifically evaluate the effect of exercise on cognitive function as the primary outcome, especially using objective outcome measures, are needed."



## Motivation for engaging in physical activity - a meta analysis

|   |                                   |          | eriment      |           |          | ontrol                           |           |                 | Std. Mean Difference                    | Std. Mean Difference                     |
|---|-----------------------------------|----------|--------------|-----------|----------|----------------------------------|-----------|-----------------|---|--|
| - | Study or Subgroup                 | Mean     | SD           | Total     | Mean     | SD                               | Total     | Weight          | IV, Random, 95% CI                      | IV, Random, 95% Cl                       |
| ł | Post-intervention                 |          |              |           |          |                                  |           |                 |   |  |
|   | Baruth 2015                       | 42       | 9.167        | 18        | 37.9     | 9.167                            | 12        | 4.2%            | 0.44 [-0.30, 1.18]                      |  |
|   | Pinto 2013a                       | 42.2     | 5.81         | 19        | 41.9     | 5.57                             | 24        | 6.3%            | 0.05 [-0.55, 0.65]                      |  |
|   | Pinto 2013b                       | 43.29    | 7.94         | 89        | 42.17    | 8.02                             | 84        | 24.1%           | 0.14 [-0.16, 0.44]                      |  |
|   | Vallance 2007                     | 43.1     | 8.9          | 84        | 42.6     | 8.7                              | 85        | 23.7%           | 0.06 [-0.25, 0.36]                      |  |
|   | Zhou 2017                         | 40.7     | 8.77         | 61        | 37       | 8.26                             | 52        | 15.8%           | 0.43 [0.06, 0.80]                       |  |
|   | Bennett 2007                      | 19       | 2.9          | 20        | 18.54    | 3.64                             | 26        | 6.7%            | 0.14 [-0.45, 0.72]                      |  |
|   | Nyrop 2017                        | 5.17     | 2.87         | 24        | 5.23     | 2.82                             | 29        | 7.8%            | -0.02 [-0.56, 0.52]                     |  |
|   | Pinto 2005                        | 72.92    | 21.41        | 39        | 57.72    | 26.2                             | 43        | 11.4%           | 0.63 [0.18, 1.07]                       |  |
|   | Subtotal (95% CI)                 |          |              | 354       |          |                                  | 355       | 100.0%          | 0.22 [0.06, 0.37]                       | ◆  |
|   | Heterogeneity: Tau <sup>2</sup> = | 0.00; Cł | $hi^2 = 7.2$ | 9, df =   | 7 (P = 0 | .40); l <sup>2</sup> :           | = 4%      |                 |   |  |
|   | Test for overall effect:          | Z = 2.76 | (P = 0.      | 006)      |          |                                  |           |                 |   |  |
|   | 3 months follow-up                |          |              |           |          |                                  |           |                 |   |  |
| 3 | Pinto 2013a                       | 40.0     | 5.00         | 10        | 10.1     |                                  |           | 44.00/          | 0.501.000.4.041                         |  |
|   |                                   | 43.3     |              | 19        |          | 5.55                             | 23        | 14.0%           | 0.59 [-0.03, 1.21]                      |  |
|   | Pinto 2013b                       | 42.6     | 7.9          | 86        | 40.71    | 8.08                             | 80        | 58.0%           | 0.24 [-0.07, 0.54]                      |  |
|   | Pinto 2008<br>Subtotal (95% CI)   | 65.14    | 28.26        | 39<br>144 | 59.64    | 21.41                            | 41<br>144 | 28.0%<br>100.0% | 0.20 [-0.24, 0.64]<br>0.27 [0.04, 0.51] |  |
|   |                                   |          |              |           |          | 50) 13                           |           | 100.0%          | 0.27 [0.04, 0.51]                       | -  |
|   | Heterogeneity: Tau <sup>2</sup> = |          |              |           | 2(P = 0) | 1.56); I <sup>z</sup> :          | = 0%      |                 |   |  |
|   | Test for overall effect:          | Z = 2.31 | (P = 0.)     | 02)       |          |                                  |           |                 |   |  |
|   | 6-9 months follow-up              |          |              |           |          |                                  |           |                 |   |  |
|   | Pinto 2013a                       | 42.3     | 5            | 19        | 41.8     | 5.55                             | 23        | 15.0%           | 0.09 [-0.52, 0.70]                      |  |
|   | Pinto 2013b                       | 42.45    | 7.97         | 84        | 40.2     | 7.91                             | 78        | 57.8%           | 0.28 [-0.03, 0.59]                      |  |
|   | Pinto 2008                        | 67.25    |              | 39        | 54.68    |                                  | 39        | 27.2%           | 0.50 [0.05, 0.95]                       |  |
|   | Subtotal (95% CI)                 | 07.20    | 20.40        | 142       | 01.00    | 2                                |           | 100.0%          | 0.31 [0.08, 0.55]                       | •  |
|   | Heterogeneity: Tau <sup>2</sup> = | 0 00· Cł | $hi^2 = 1.2$ |           | 2 (P = 0 | (55) <sup>•</sup> l <sup>2</sup> |           |                 |   | -  |
|   | Test for overall effect:          |          |              |           | - ( 0    |                                  | 0 /0      |                 |   |  |
|   | root ion or of all offoot.        | 2.01     | 0.           | )         |          |                                  |           |                 |   |  |
|   |                                   |          |              |           |          |                                  |           |                 |   |  |
|   |                                   |          |              |           |          |                                  |           |                 |   | -2 -1 0 1 2                              |
|   |                                   |          |              |           |          |                                  |           |                 |   | Favours [control] Favours [experimental] |

Supporting and counselling seem to be very important for the effect

FIGURE 2-Forest plot of the meta-analysis on fatigue after the intervention (A) at follow-up of 3 months (R) and at follow-up of 6 to 9 months (C) CI confidence interval.

|   |   | Experimental  |  | c                     | Control                    |                              |                      | Std. Mean Difference                      | Std. Mean Difference             |   |   |
|---|---|---|--|-----------------------|----------------------------|------------------------------|----------------------|---|----------------------------------|---|---|
|   |   | Study or Subgroup   | Mean   | SD                    | Total                      | Mean                         | SD                   | Total                                     | Weight                           | IV, Random, 95% C   | IV, Random, 95% CI                                      |
|   | A | No/infrequent counseling  |  |                       |                            |                              |                      |   |                                  |   |   |
|   |   | Vallance 2007   | 43.1   | 8.9                   | 84                         | 42.6                         | 8.7                  | 85  | 63.4%                            | 0.06 [-0.25, 0.36]  | -   |
|   |   | Bennett 2007  | 19   | 2.9                   | 20                         | 18.54                        | 3.64                 | 26  | 16.9%                            | 0.14 [-0.45, 0.72]  |   |
|   |   | Nyrop 2017  | 5.17   | 2.87                  | 24                         | 5.23                         | 2.82                 | 29  |                                  | -0.02 [-0.56, 0.52]   |   |
|   |   | Subtotal (95% CI)   |  |                       | 128                        |                              |                      | 140                                       | 100.0%                           | 0.05 [-0.19, 0.29]  | +   |
|   |   | Heterogeneity: Tau <sup>2</sup> =   |  |                       |                            | 2(P = 0                      | .93); I <sup>2</sup> | = 0%                                      |                                  |   |   |
|   |   | Test for overall effect:  | Z = 0.45   | (P = 0.               | 66)                        |                              |                      |   |                                  |   |   |
| HUIZINGA F et al. Med Sci Sports Exerc<br>2021 Dec 1;53(12):2661-2674 | В | Frequent counseling<br>Baruth 2015<br>Pinto 2013a<br>Pinto 2013b<br>Zhou 2017<br>Pinto 2005<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect: | 42<br>42.2<br>43.29<br>40.7<br>72.92<br>0.01; Ch | 7.94<br>8.77<br>21.41 | 61<br>39<br>226<br>1, df = | 41.9<br>42.17<br>37<br>57.72 |                      | 12<br>24<br>84<br>52<br>43<br>215<br>= 9% | 10.7%<br>37.6%<br>25.6%<br>18.9% | 0.44 [-0.30, 1.18]<br>0.05 [-0.55, 0.65]<br>0.14 [-0.16, 0.44]<br>0.43 [0.06, 0.80]<br>0.63 [0.18, 1.07]<br>0.32 [0.12, 0.52] |   |
|   |   | Test for subgroup diffe   |  | 01-12 - 0             | . 70 . 44                  | - 1 (D                       | 0.40                 | 12 - 00                                   |                                  |   | -2 -1 0 1 2<br>Favours [control] Favours [experimental] |



Test for subgroup differences: Chi<sup>2</sup> = 2.70, df = 1 (P = 0.10), l<sup>2</sup> = 62.9%

FIGURE 3-Forest plot of the meta-analysis on fatigue for no or infrequent counseling (A) and frequent counseling (B). CI, confidence interval.

# Different type of physical training

- In a meta analysis of 20 randomized clinical trials involving 1793 participants it was found that:
  - supervised combination of resistance training (RT) with aerobic training (AT) is the most effective physical exercise to reduce fatigue
  - the supervised RT was more effective than supervised AT or mind– body techniques.

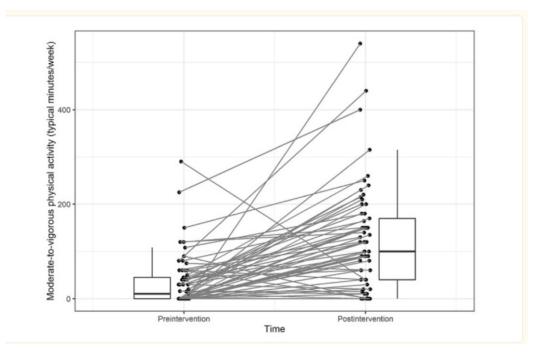
Medeiros Torres D et al. Supportive Care in Cancer (2022) 30:4651–4662



## Can this be done via the Internet

• A study of 82 breast cancer survivors,

testing a internet based intervention based on the "Acceptance and Commitment Therapy" (ACT)



Robertson MC et al: JMIR Cancer. 2022 Apr-Jun; 8(2): e31815



# Barriers for engaging in physical activity

- The participation rate in physical activity programs is often low
  - Lack of time
  - Lack of motivation
  - Lack of confidence (in how to perform training)
  - Feeling unwell or tired



## Targeting activity or sedentary time

- In a study of 199 breast cancer survivors, where both amount of physical activity and sedentary time was assessed:
  - Moderate to vigorous physical activity let to decreased depressive symptoms
  - Sedentary time predicted level of pain and depressive symptoms
  - More sedentary time higher scores on pain and depression

Dore I et a.l Supportive Care in Cancer vol 30, 785–792 (2022)



# **Relevant end points**

- Quality of life
- Patient reported outcome
  - Fatigue
  - Pain
  - Depressive symptoms
- Objective measurements
  - Muscle strength
  - Cardiorespiratory fitness
  - Sedentary time?



## Challenges when drawing conclusions

- Small sample sizes
- Many different end-points
- Different measures
- Different intervention



# Conclusion

- Physical activity is a promising intervention
- Physical activity seem to be able to alleviate late effects
  - It is cheap
  - It is with-out side effects
- Possibilities for (supervised) physical activity should be established
- More knowledge about what kind of physical activity is most effective



# Thank you for Your attention

# **Questions** !

