

Cardiovascular function and the effect of exercise training during adjuvant breast cancer treatment. Results from The EBBA-II trial (NBCG-14)

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On behalf of the **E**nergy **B**alance and **B**reast Cancer **A**spect study group



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DECEMBER 4-8

HENRY B. GONZALEZ CONVENTION CENTER,
SAN ANTONIO, TEXAS, USA

Dr. Thune has no relevant financial relationships with commercial interests to disclose.

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Background



Ramazzini (1633–1714) prescribed **exercise**: rest and a walk in the fresh air



Hippocrates (460-375 BC) «Walking is the man's best medicine»

The risk of cardiovascular disease following breast cancer by Framingham risk - EPIC-NL

Women with breast cancer vs non-breast cancer women higher risk of CVD morbidity and mortality
Gernaat et al, 2018

Heart failure induced by cancer therapy vs heart failure not induced by cancer therapy worse long-term prognosis

Nadrush et al 2018

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Background

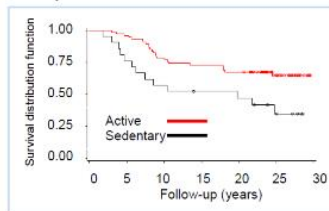
Energy Balance and Breast Cancer Aspects Studies EBBA-I, EBBA-II, EBBA-life

EBBA-I

Healthy women 25-35 yrs lifestyle, genetic pre-disposition, oestrogen and progesterone levels and mammographic density

EBBA-life

Population based cohort study



Emaus, Thune et al 2009

EBBA-II

A Randomised Exercise Trial
(NCT02240836)



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Objectives

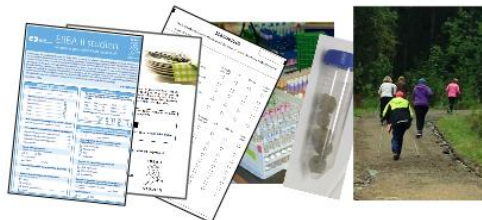
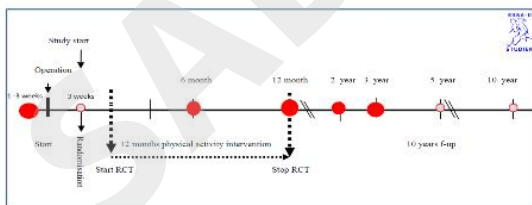
Primary

- To determine whether a **12-month exercise program** comprised of **endurance** and **strength training** during adjuvant therapy influence **cardiopulmonary function**.
- Evaluate the **efficacy** and **safety profile** of the **exercise program during adjuvant breast cancer treatment**
- To determine the recommended type, dose, intensity and duration of exercise



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Study Assessments (2011 (june)-2018)



The exercise intervention 12 months:

- 3 weeks post-surgery
- Group based (10-12 women)
- Detailed training program
- Outdoor: moderate-high intensity, stretching, weight bearing
- 60 min x 2/week + 120 min at home (240 min/weekly)
- Lead by physiotherapists

Control: standard of care, no restrictions



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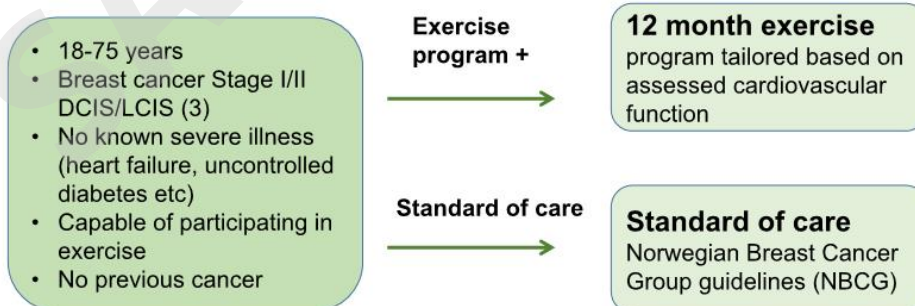
Study Assessments

- **Screening**
 - **Information** by trained nurses at three outpatient clinics in Norway
 - Invitation by phone calls (physicians)
 - **Cardiovascular capacity** assessed using the
 - same protocol and trained personnel
- **Randomisation:** 3 weeks **after surgery**
- **VO₂ max;** **before surgery, 6 months and 12 months**



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Study Design: EBBA-II (NBCG-14 study)



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Cardiopulmonary Exercise Test (CPET)

- Non-invasive **evaluation of the cardio-vascular system during exercise** on a treadmill until exhaustion
 - **Stepwise modified Balke** protocol (Borg scale 6–20)
 - Assessments of gas exchange, HR, BP, blood lactate, SPO₂
 - **Evaluation of cardiovascular system:** heart failure, myocardial ischemia, cardiac valve function, chronotropic incompetence
- **Before surgery, 6 and 12 month**



*Balke . U S Armed Forces Med J . 1959, Edvardsen, Chest 2013 ;
Nadruz W, Heart, 2018-313234*

2018 San Antonio Breast Cancer Symposium

December 4-8, 2018

Statistical Consideration

Design EBBA-II trial: randomized, assessor blinded, controlled, parallel-group, multi-center, single-country, superiority study.

- a computer randomization procedure
- stratified by pre- vs post-menopausal status

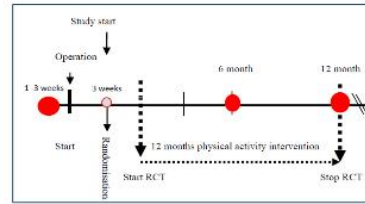
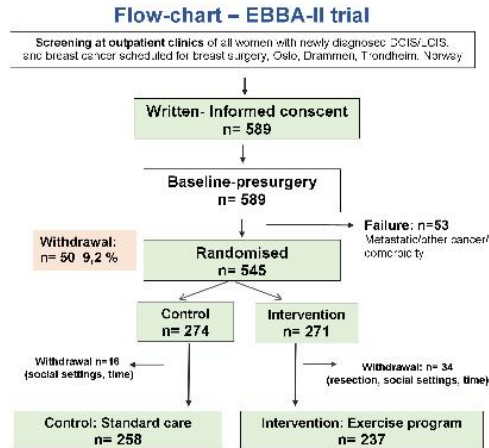
Primary outcome: **change in VO_{2max}, baseline - 12 months.**

- linear mixed model: baseline, 6 months, and 12 months, **plots of VO_{2max}** on the y-axis and time on the x-axis.
- **Primary analysis:** full analysis set (modified intention to treat analysis).

R version 3.5.1 (2018-07-02), R Core Team (2018), <https://www.R-project.org/>

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Enrollment and participation



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Baseline Characteristics

Characteristics	Exercise intervention (n = 271) Mean(SD)	Standard Care (n = 274) Mean(SD)
Age, yrs	55.2 (9.7)	55.6 (9.7)
Education, yrs	15.4 (3.3)	15.0 (3.4)
Age at menarche, yrs	13.2 (1.4)	13.1 (1.3)
SBP, mmHg)	129 (21)	130 (20)
DBP, mmHg)**	75 (11)	75 (10)
BMI, kg/m ²)	25.6 (4.3)	25.6 (4.6)
<i>Tumor characteristics</i>		
Invasive Breast Carcinoma NST, %	71.6 (194)	72.3 (198)
Invasive Lobular carcinoma, %	12.9 (35)	11.7 (32)
Ductal/Lobular Carcinoma In Situ, %	7.0 (19)	5.1 (14)
Other, %	8.5 (23)	10.9 (30)
<i>Histologic grade, %</i>		
1	25.0 (65)	28.2 (70)
2	46.5 (121)	43.1 (115)
3	28.5 (74)	30.7 (82)
Tumor diameter, mm	17.7 (11.0)	17.1 (9.9)
Lymph node metastasis, %	22.7 (56)	22.1 (58)
ER positive, %	88.3 (219)	86.5 (225)
PgR positive, %	71.8 (178)	68.2 (176)
Ki67, %	22.6 (29.1)	24.4(30.3)
Her 2 positive, %	13.0 (32)	13.8 (36)

*Number may vary due to missing values, **SBP/DBP: mean of two last measurements.
***- 1=histological 1= tamoxifen 1= Cyclophosphamide



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Baseline Characteristics

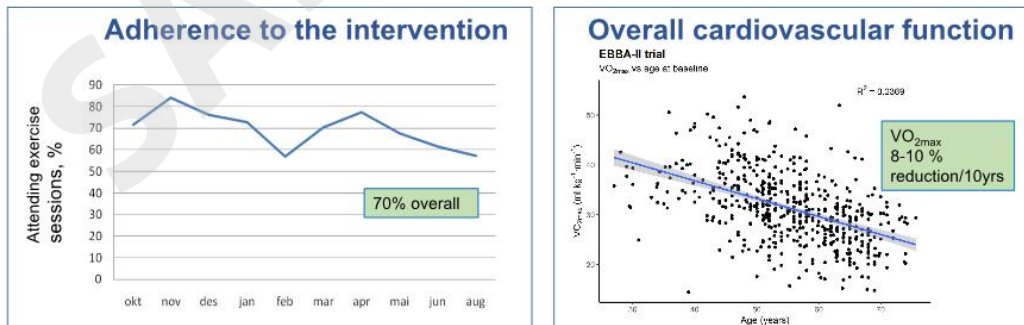
Characteristics	Exercise intervention (n = 271) mean/% (n/SD)	Standard Care (n = 274) mean/%(n/SD)
Treatment (%)		
<i>Surgery</i>		
BCT	68.9 (184)	74.4 (201)
Sentinel node examination (SN)	85.0 (226)	85.9 (232)
Axillary dissection	12.8 (34)	11.9 (32)
<i>Chemotherapy</i>		
Anticycline regimen (FEC/EC ^{***})	55.1 (147)	54.8 (148)
Taxanes	53.9 (144)	53.7 (145)
39.3 (105)		39.6 (107)
<i>Radiation therapy (%)</i>		
76.8 (205)		84.7 (227)
<i>Endocrine therapy (%)</i>		
59.9 (160)		55.8 (150)
Cardiorespiratory fitness		
VO _{2max} (L/min)	2.17 (0.43)	2.22 (0.43)
VO _{2max} (ml/kg/min)	31.0 (6.8)	31.7 (7.4)

* Number may vary due to missing values,**F: 5-Flurouracil E:Epirubicin :C,Cyclophosphamide



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Adherence and Adverse Events (AE) Cardiovascular capacity (VO_{2max})

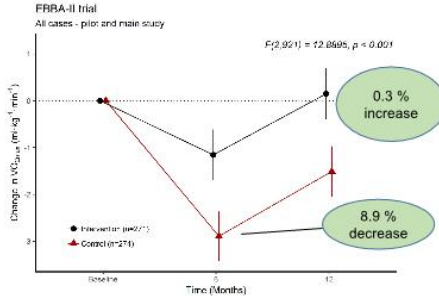


AE's: Fatigue during CPET/exercise, one injured shoulder

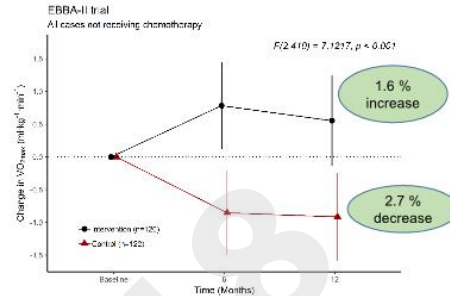
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Final results - The EBBA-II (NBCG-14)

All participants (n= 545)



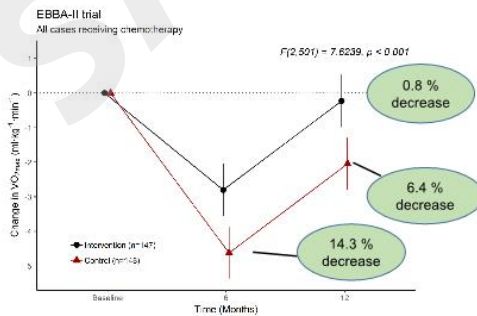
No chemotherapy (n=242)



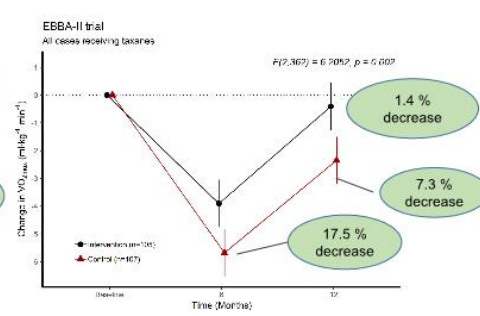
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Patients receiving chemotherapy

Receiving chemotherapy (n= 295)



Receiving taxanes (n= 212)



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Summary and Conclusions

- The EBBA-II trial met its primary endpoint in the exercise group
- All subgroups of patients benefited from physical activity during breast cancer treatment
- Our study supports incorporation of supervised and safe clinical exercise programs into breast cancer treatment guidelines
- Future direction: breast cancer patient receiving chemotherapy should be offered tailored exercise program based on assessed pre-treatment level of physical function



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Thank You

Thank you to all 545 breast cancer patients and their families

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