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 Energy Balance and Breast Cancer Aspect study group

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**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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Energy Balance and Breast Cancer Aspects Studies

**EBBA-I, EBBA-II, EBBA-life**

**EBBA-I**
Healthy women 25-35 yrs lifestyle, genetic predisposition, oestrogen and progesterone levels and mammographic density

**EBBA-life**
Population based cohort study

**EBBA-II**

A Randomised Exercise Trial

(NCT02240836)

Ennaas, Thune et al 2009

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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

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)

- 18-75 years
- Breast cancer Stage I/II DCIS/LCIS (3)
- No known severe illness (heart failure, uncontrolled diabetes etc)
- Capable of participating in exercise
- No previous cancer

Exercise program + 12 month exercise program tailored based on assessed cardiovascular function

Standard of care Norwegian Breast Cancer Group guidelines (NBCG)

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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


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 VO₂max, baseline - 12 months.
- linear mixed model: baseline, 6 months, and 12 months, plots of VO₂max 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

Flow-chart - EBBA-II trial

- Written informed consent: 580
- Baseline pre-surgery: 569
- Randomised: 568
- Control: Standard care: 258
- Intervention: Exercise program: 237

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Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exercise, Intervention (n=271) Mean(SD)</th>
<th>Standard Care (n=274) Mean(SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>55.2 (9.7)</td>
<td>55.8 (9.7)</td>
</tr>
<tr>
<td>Education, yrs</td>
<td>15.4 (3.3)</td>
<td>18.0 (3.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.6 (4.3)</td>
<td>25.5 (4.0)</td>
</tr>
<tr>
<td>Tumor characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive Breast Carcinoma, %</td>
<td>71.6 (194) 72.3 (198)</td>
<td></td>
</tr>
<tr>
<td>Invasive Lobular carcinoma, %</td>
<td>12.9 (28) 11.7 (22)</td>
<td></td>
</tr>
<tr>
<td>Ductal/ Lobular Carcinoma in situ, %</td>
<td>7.0 (18) 5.1 (14)</td>
<td></td>
</tr>
<tr>
<td>Others, %</td>
<td>8.5 (25) 10.9 (30)</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin, g/dL</td>
<td>12.6 (0.35) 12.1 (0.70)</td>
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Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Exercise Intervention (n = 271) mean/SD</th>
<th>Standard Care (n = 271) mean/SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment (%)</td>
<td></td>
<td></td>
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<tr>
<td>Surgery</td>
<td>58.8 (164)</td>
<td>74.4 (201)</td>
</tr>
<tr>
<td>Sentinel lymph-node dissection</td>
<td>85.0 (226)</td>
<td>85.9 (232)</td>
</tr>
<tr>
<td>Axillary dissection</td>
<td>12.6 (34)</td>
<td>11.9 (32)</td>
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<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracycline regimen ( FECET®)</td>
<td>53.9 (144)</td>
<td>53.7 (140)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>39.5 (103)</td>
<td>39.6 (107)</td>
</tr>
<tr>
<td>Radiation therapy (%)</td>
<td>76.8 (203)</td>
<td>64.7 (227)</td>
</tr>
<tr>
<td>Endocrine therapy (%)</td>
<td>59.5 (169)</td>
<td>55.6 (150)</td>
</tr>
<tr>
<td>Cardiorespiratory fitness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VO_{max} (L/min)</td>
<td>2.17 (0.43)</td>
<td>2.22 (0.43)</td>
</tr>
<tr>
<td>VO_{max} (W/kg/m²)</td>
<td>31.0 (5.6)</td>
<td>31.7 (7.4)</td>
</tr>
</tbody>
</table>

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

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

**Adherence to the intervention**

**Overall cardiovascular function**

**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)

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

Thank You

Thank you to all 545 breast cancer patients and their families

Site PIs, physicians, physiotherapists, exercise physiologists, nurses, data and trial coordinators, and pathologists, the participating centers in Oslo, Drammen and Trondheim

Norwegian Breast Cancer Group – NBCG-14 study
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