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Rationale and description of a lifestyle intervention programme to achieve moderate weight loss in women with non-metastatic breast cancer: the lifestyle intervention part of the SUCCESS C Study

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ABSTRACT

Objective There is growing evidence from observational studies that lifestyle factors such as obesity, an unhealthy diet and lack of physical activity are associated with poor long-term outcome in women with breast cancer. The primary objective of the lifestyle modification part of the Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation, as well as Life Style Intervention Strategies (SUCCESS C) Trial is to investigate the effect of an individualised lifestyle intervention programme aiming at moderate weight loss on disease-free survival in women with HER2/neu-negative breast cancer. Secondary objectives include the effect of the intervention on body weight, cardiovascular risk and quality of life.

Methods The SUCCESS C Trial is an open-label, multicentre, randomised controlled phase III study using a 2×2 factorial design in women with newly diagnosed HER2/neu-negative intermediate-risk to high-risk breast cancer. The first randomisation served to compare disease-free survival in patients treated with two different chemotherapy regimens (3642 participants). The second randomisation served to compare disease-free survival in patients with a body mass index of 24–40 kg/m² (2292 participants) receiving either a telephone-based individualised lifestyle intervention programme for moderate weight loss or general recommendations for a healthy lifestyle for 2 years. Outcome analyses will be conducted after 5 years of follow-up.

Perspective This study will provide information on the efficacy and safety of a comprehensive lifestyle intervention programme on disease-free survival in a large cohort of women with breast cancer. EU Clinical Trials Identifier: 2008-005453-38.

What this paper adds

- There is limited evidence that lifestyle is relevant for the prognosis of breast cancer.
- Weight loss in women with breast cancer improves potential biomarkers of disease progression.
- Randomised controlled intervention trials are urgently needed to explore the potential of comprehensive lifestyle modification on breast cancer survival.
- This paper describes the lifestyle intervention programme of the SUCCESS-C trial.

INTRODUCTION

There is growing evidence from a variety of observational studies that lifestyle factors contribute substantially to the risk of developing breast cancer. These factors include an unhealthy diet and a lack of physical activity, and overweight/obesity.[1–3]

While the database for primary prevention of breast cancer is considerable, there is much less information on the role of lifestyle factors for the prognosis of women with diagnosed breast cancer. The evidence for similar associations between lifestyle factors mentioned and mortality from breast cancer is limited, as the risk of relevant confounding is substantial in many studies.[4] However, the conclusion of many systematic reviews and meta-analyses was that greater body fatness, measured by weight and body mass index (BMI), is significantly associated with increased mortality.[5–7]

Although observational studies have linked obesity and poor lifestyle to a poorer outcome of breast cancer, there is an urgent need to perform randomised controlled trials, as it is not fully clear if the reported associations are causal and to what extent lifestyle changes may affect cancer prognosis. To date, most lifestyle intervention studies are small and have mainly evaluated their effect on quality of life or intermediate end points such as biomarkers linked to breast cancer.[8]

There is also only a small number of clinical studies on the effect of weight loss in women with breast cancer.[9 10] Two large-scale intervention studies initiated in the 90s have examined the effect of reduction in fat intake on breast cancer recurrence and mortality. In the Women's Intervention Nutrition (WIN) Study women with breast cancer received an intervention focussing on the reduction of fat intake. After a follow-up of 5 years a reduction of relapse events was observed compared with the control group (HR of 0.76 (p=0.034 for adjusted Cox model analysis)).[11] In contrast, the Women's Healthy Eating and Living (WHEL) Trial observed no effect of a diet low in fat and high in vegetables, fruit and fibre on breast cancer recurrence or mortality.[12] A potential explanation for these discrepant findings may be that WIN—in contrast to WHEL—observed a modest weight loss, which might have influenced the outcome. Both studies did not consider other lifestyle components such as physical activity and management of obesity.

Therefore, the aim of this study was to investigate the effect of a comprehensive lifestyle intervention programme including a healthy, moderately hypocaloric diet and an increase in physical activity on the prognosis of breast cancer in women at intermediate risk to high risk. This article describes the design and procedures of the lifestyle modification part of the study in detail.

METHODS

Study design

The SUCCESS C Study (acronym for 'Simultaneous Study of Docetaxel Based Anthracycline Free Adjuvant Treatment Evaluation, as well as Life Style Intervention Strategies') is an open-label, multicentre, randomised, controlled phase III study in women with newly diagnosed HER2/neu-negative breast cancer. There were two randomisations after recruitment: a first randomisation for chemotherapy and a second randomisation for the lifestyle intervention part, confined to women with a BMI between 24 kg/m^2 and 40 kg/m^2, thereby representing a 2×2 factorial design. A first description of the SUCCESS C Study detailing chemotherapy and endocrine treatment was published previously.[13] Randomisation was performed after surgical treatment when the inclusion criteria were met and the written informed consent form was signed by the patient.

Primary objectives

The primary objectives of the SUCCESS C Trial were:

- To compare disease-free survival in patients treated with a combination of 5-Fluorouracil/epirubicin/cyclophosphamide followed by docetaxel or docetaxel/cyclophosphamide continuously.
- To compare disease-free survival after randomisation of patients into a comprehensive and individualised lifestyle intervention programme (aiming at moderate weight loss) or general lifestyle recommendations.

Disease-free survival was defined as the time from randomisation to the diagnosis of locoregional recurrence, distant metastases or death. Locoregional recurrence was defined as any relapse in the area of primary surgery and/or ipsilateral regional axillary lymph nodes including the nodules of the infraclavicular or supraclavicular fossa. Any other tumour manifestation was defined as distant disease. As cardiometabolic disease is the major cause of death in women of this age and as women with breast cancer may also benefit from an improvement in cardiovascular risk factors, we were also interested to study changes in cardiovascular risk, in addition to changes in body weight.

Secondary objectives

- Changes in body weight and waist circumference.
- Changes in blood pressure and cardiometabolic risk factors (blood glucose, HbA1c, total, low density lipoprotein-cholesterol and high density lipoprotein-cholesterol, triglycerides).
- Clinical manifestation of type 2 diabetes, hypertension and cardiovascular disease.
- Changes in dietary habits and patterns and in physical activity.
- Change in health-related quality of life.
- Change in Eastern Cooperative Oncology Group performance status.
- Change in biomarkers (eg, adiponectin, insulin).

Study population

Participant enrolment

In total, 3642 participants have been enrolled between February 2009 and August 2011. Finally, 231 recruiting study centres throughout Germany were contributing to the study. Two thousand two hundred and ninety-two participants with a BMI of 24–40 kg/m² (63% of total participants) were randomised for the lifestyle intervention part of the study.

Patients were recruited into the study not later than 6 weeks after complete surgical resection of the primary tumour.

Eligibility criteria

Inclusion criteria

Eligible patients had to meet the following criteria:

- Women ≥18 years of age.
- Primary epithelial invasive carcinoma of the breast $pT_{1–4}$, $pN_{0–3}$, pM_0.
- No evidence of HER2-neu overexpressing (IHC neg or +) or amplifying (FISH−) tumour.
- Histopathological proof of axillary lymph node metastases ($pN_{1–3}$) or high-risk node negative, defined as at least two criteria of the following: pT ≥2, histopathological grade 3, age ≤35, negative hormone receptor.
- Complete resection of the primary tumour with margins of resection free of invasive carcinoma not more than 6 weeks ago.

- Willingness to participate in a telephone-based lifestyle intervention programme.
- Ability to understand the nature of the study and to give written informed consent.

Exclusion criteria

Patients were excluded from the study for any of the following reasons:

- Inflammatory breast cancer.
- Cardiomyopathy with impaired ventricular function (New York Heart Association (NYHA) >II), cardiac arrhythmias influencing left ventricular ejection fraction and requiring medication, history of myocardial infarction or angina pectoris within the last 6 months, or arterial hypertension not being controlled by medication.
- Patients in pregnancy or lactation (in premenopausal women, anticonception had to be assured).
- Insulin-requiring diabetes mellitus (non-insulin-requiring patients with type 2 diabetes were eligible for the study).
- Serious digestive and/or absorptive problems that exclude adherence to the dietary recommendations of the study.
- Self-reported inability to walk at least 1 km (at any pace).
- Cardiovascular, respiratory or musculoskeletal disease or joint problems that precluded moderate physical activity.
- Psychiatric disorders or conditions that would preclude active participation.
- Patients not sufficiently fluent in German language to understand the nature of this study.

Randomisation

Both first (chemotherapy treatment) and second (lifestyle intervention) randomisation took place at the time between resection of the primary tumour and the start of chemotherapy. All enrolled patients with a BMI of 24–40 kg/m² were randomised for the lifestyle intervention. Randomisation was balanced between the two study arms (1:1) and performed using a block size of 4. While the first randomisation for chemotherapy treatment was stratified for axillary lymph node involvement, hormone receptor status, histopathological grading, menopausal status and patient BMI, no stratification was implemented with regard to the second randomisation to individualised lifestyle intervention versus general lifestyle recommendations.

The lifestyle intervention programme

The lifestyle intervention programme of the SUCCESS C Trial was based on the Diabetes Prevention Programme (DPP).[14] The detailed intervention manual of DPP is available online (http://www.bsc.gwu.edu/dpp/manuals.html.doc).

For the purpose of this study, the DPP was modified according to new developments in weight management and the specific requirements of the study. New elements included principles to lower energy density to better maintain satiety,[15] a greater focus on reducing sugar-sweetened beverages and a more individualised approach with greater flexibility to consider individual preferences. Furthermore, the intervention was culturally adapted to the lifestyle and eating habits in Germany as well as to the special situation of women with breast cancer. Nutrition recommendations were adapted according to the World Cancer Research Fund (WCRF),[1] for example, for limitation on or renouncing alcohol consumption, for fat reduction, for limitation of red meat and processed meat, for sufficient intake of protein, for enhancing intake of fibre, fruit and vegetables. High-caloric soft drinks—also fruit juice—should be avoided, preferring low-caloric or calorie-free beverages. Physical activity recommendation was adapted to the individual situation. The team of coaches was additionally supervised by a psycho-oncologist to be aware of the psychological situation and problems of patients with breast cancer.

For applicability reasons, the programme was transformed into a semistructured telephone-based intervention mode supplemented with detailed information and training material and newsletters sent by mail. As participants were living disseminated over the country and were recruited through a 3-year period, the telephone-based intervention was considered as an adequate way to provide the lifestyle programme in a highly standardised manner. The 2-year lifestyle intervention programme was planned to start 3 months or 6 months after the end of chemotherapy to allow physical recovery.

Goals of the intervention

The weight loss goal of the intervention should be achieved after 6 months, defined as a moderate reduction of body weight by 5% (not more than 10 %) at a baseline BMI of 24–29.9 kg/m² and by 10% (not more than 20%) at a baseline BMI of 30–40 kg/m² with subsequent weight maintenance. Participants should not fall below a BMI of 22 kg/m².

Key components of the intervention

The intervention programme comprised the following components:

1. A moderate caloric restriction with an estimated energy deficit of 500 kcal per day. The level of recommended caloric intake was between 1200 kcal and 1800 kcal per day based on the calculation of energy expenditure, using a formula developed for the adult German population.[16]
2. The diet included a fat reduction to 20%–25% of the total energy intake. At the same time, the intake of wholegrain products, fruit and vegetables should be increased. Targets for fruit intake were two to three portions at 150 g/day. Targets for vegetables were two to three portions at 200–300 g/day. Other targets for dietary intake were two to three portions of dairy products per day, two to three portions (100–150 g) of fish

per week, two to three portions (100–150 g) of meat per week, very small amounts of processed meat (maximum 20–30 g/day). Rapeseed and olive oil as well as diet margarine should be preferred. Women were encouraged to limit alcohol consumption to a maximum 10 g per day for 3 days a week if acceptable.

3. An increase in physical activity was intended tailored to the individual fitness with brisk walking as the main recommendation. Participants were advised to practise regular physical activity of moderate intensity, at least 150 min per week.
4. Regular self-monitoring and recording of body weight—at least once a week—was advised.
5. Additionally the intervention included behavioural components based on cognitive social therapy,[17] such as maintaining motivation, overcoming obstacles to success, relapse prevention, emotional distress management with preprints for documentation of the participants.

Following the DPP, women assigned to the lifestyle intervention part received 19 telephone calls from their lifestyle coaches during the 2 years. Up to three additional calls were offered by the coaches in case of a need to reinforce aspects of the intervention or dealing with barriers to success. The 19 telephone calls with a mean duration of 30 min were scheduled as follows:

(1) Intensive phase (month 1): weekly for weeks 0, 1, 2, 3, 4; (2) Consolidation phase (month 2–6): every 2 weeks for months 2 and 3, monthly for months 4–6; (3) Maintenance phase (months 7–24): every 2 months for months 7–12, every 3 months for months 13–24. Consequently, during the first 6 months there were at least 12–13 calls plus a welcome call and up to 3 calls optionally. The telephone calls were standardised and semistructured according to DPP (concerning topics and intervals) and conducted by specifically trained lifestyle coaches from almeda GmbH, a medical service centre in Munich which is specialised in the delivery of telephone-based disease management and lifestyle modification programmes. The lifestyle coaches had primary qualification such as dieticians, ergotherapists or nurses and were receiving continuous training in communication techniques. Five per cent of the telephone calls were supervised. Every effort was made to keep the same lifestyle coach for individual participants throughout the study. In case of severe psychological problems of participants, a psycho-oncologist was available for immediate intervention.

Support material for the participants of the intervention group

Based on the DPP manual, the support material for the intervention group contained

- A detailed manual with 16 different chapters referring to the corresponding telephone calls containing key messages.
- A fat counter in the form of a booklet informing about the fat content of foods/meals.
- A workbook with instructions and self-monitoring tools (eg, eating habits, physical activity).
- A newsletter sent at 6 months and 18 months.
- For the solution of obstacles confronting individual participants, the coaches also had access to a toolbox including for example, gymnastic articles, cookbooks or other gifts.

Initiation and implementation of the intervention

After confirmation by the study doctor a 'starter-package' was handed over to the women. The main constituents of the 'starter-package' were a preprint of a 7-day dietary record including a physical activity record as well as a pedometer. Patients were encouraged to record their dietary intake and physical activity. This baseline information was used to tailor the lifestyle programme to the individual wishes and needs of the patient.

Control group

The patients of the control group received a standardised mail-based low-level intervention focussing on healthy living. This programme included mailings at study entry and 12 months later with general information on a healthy lifestyle. Additionally, the participants allocated to the control group received a 1 year free subscription to 'Vital', a monthly German health magazine.

Data collection

Baseline and follow-up assessment for the lifestyle intervention study

A physical examination at baseline was performed in the local study centre as well as during all follow-up examinations at months 6, 12, 24 and after 48 months. Women of the intervention group and control group underwent the following measurements at the local study centre:

Height to the nearest 0.5 cm, weight to the nearest 100 g (in indoor clothing without shoes), waist circumference using a flexible tape midway between the lower rib margin and the iliac crest with the patient in a standing position and normal breathing, blood pressure at rest and fasting blood sampling. Dietary intake was assessed using 7-day dietary records. Physical activity was assessed using the International Physical Activity Questionnaire (International Physical Activity Questionnaire (IPAQ), German version).[18] Health-related quality of life was measured using the following questionnaires: The Hospital Anxiety and Depression Score (HADS) Questionnaire ('Hospital Anxiety and Depression Scale'),[19] the European Association for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, combined with the special module for breast cancer EORTC QLQ-BR23,[20] and the 'Belastungsthermometer' Questionnaire.[21] All questionnaires were sent out 4 weeks prior to the follow-up examinations.

Blood collection

During the regular visits in the local study centres, fasting blood samples were collected and handled according to predefined standard operation procedures (SOPs) for the measurement of routine and safety parameters. In addition, serum and plasma biosamples were stored in

the study centres at –20°C, then rapidly transferred to the central biobank and kept at –80°C.

Safety, documentation and data management

All adverse events were documented by the study centres and reported to the study coordinator board. The independent Data Monitoring and Safety Board was regularly informed about any safety issues. All data on patient recruitment and treatment, anthropometric and laboratory variables, blood pressure as well as on medication and concomitant diseases were documented in a central databank.

Discontinuation of the lifestyle intervention

The weight management programme was stopped in the following situations:

- Any medical circumstance considered reasonable by the treating study doctor or another primary physician (eg, new onset of congestive heart failure).
- Disease recurrence: women who experienced ipsilateral or locoregional breast cancer events or new contralateral breast cancer primaries or distant metastasis have met the primary study outcome and were withdrawn from the study (for safety reasons).
- Development of a non-breast primary invasive tumour was handled in a manner similar to disease recurrence.
- Request by the patient.

Feasibility evaluation

Before starting the intervention, a pilot run involving 20 female staff members—with no history of breast cancer—was conducted to get feedback on the lifestyle modification programme for clarity, comprehension and ease of use. Comments were discussed and minor changes were made to improve the programme, mainly with regard to understandability and feasibility (data not shown).

Statistical analysis

According to the sample size calculation based on the chemotherapy intervention, SUCCESS C was planned to recruit 3546 participants with an accrual time of 3 years and a follow-up period of 5 years from the end of acrual. It was expected that 62% of all participants entering the trial have a baseline BMI ≥24 kg/m², resulting in 2198 patients entering the lifestyle intervention. With this sample size there is a power of 80% to detect a difference of 6% in disease-free survival rates at 5 years.

The 5-year disease-free survival rate will be compared between the two lifestyle intervention arms using the χ^2 test. Median disease-free survival will be assessed using the Kaplan-Meier method and compared using the log-rank test. Multivariable Cox regression models adjusted for other factors known to affect survival will be used to test whether there is an independent effect of lifestyle intervention on survival. Secondary outcomes will be evaluated with mixed models for repeated measurements adjusting for baseline weight, chemotherapy and BMI. All analyses will be performed using the statistical programme SPSS, V24.0 (IBM Corp, Armonk, New York, USA).

DISCUSSION

Despite growing evidence from observational studies that lifestyle factors such as elevated body weight, lack of physical activity and a poor diet negatively influence the prognosis of women with breast cancer,[4 6 22] there are little data available as to whether lifestyle intervention programmes can affect survival in patients with breast cancer. To date, only two large-scale randomised controlled intervention studies have tried to examine the effect of lifestyle intervention on breast cancer prognosis with conflicting results.[11 12] A general disadvantage of both studies was that the intervention programmes were not comprehensive and did not include important lifestyle components, for example, increase in physical activity.

Previous observational studies and meta-analyses have provided limited evidence for a positive influence of weight reduction on prognosis,[1 5] but this is not yet proven by an intervention trial. Therefore, the lifestyle intervention part of the SUCCESS C Study was designed to focus on weight loss in newly diagnosed women with intermediate-risk to high-risk breast cancer. The available data justify the inclusion of premenopausal as well as postmenopausal women,[5 23] regardless of the receptor status.[24]

The central components of the intervention programme included a moderate energy restriction, a healthy diet and an increase in moderate physical activity to at least 150 min per week to achieve a moderate weight loss of 5%–10%.[3 4] Waist circumference was measured as an indicator of the fat distribution pattern which is considered as risk factor for breast cancer.[1] A limitation of the study is that we did not assess body composition by established methods.

To minimise the frequently observed weight regain the lifestyle intervention programme comprised regular self-monitoring of weight, diet, physical activity and behaviour as well as a special focus on behavioural aspects, for example, motivation training, overcoming obstacles, relapse prevention. Recording of diet and physical activity for self-monitoring was recommended daily during the first 6 months and later on optionally.

In recent years, a number of weight loss intervention studies with mostly small sample sizes and short duration of follow-up have been performed in women with breast cancer.[9 10] Most of these studies evaluated changes in body weight and quality of life or biomarkers linked to cancer risk, but not hard end points such as disease-free survival.[8 25 26]

Recently, the results of two larger weight loss trials with longer intervention periods were published. In the lifestyle intervention in adjuvant treatment of early breast cancer study (LISA) Trial, using a similar protocol as the SUCCESS C Study, 338 women with early breast cancer were included and underwent a 2-year telephone-based weight loss and maintenance programme. Mean weight loss after 24 months was 3.1% vs 0.4% in the control group.[27] In the Exercise and Nutrition Enhance Recovery and Good health for You (ENERGY) Trial, a behavioural

weight loss intervention in 692 overweight or obese breast cancer survivors resulted in a mean weight reduction of 3.7% in the intervention group compared with 1.3% in the control group.[28]

In the SUCCESS C Study, the lifestyle intervention programme was provided as a semistructured telephone-based intervention supplemented with detailed materials and newsletters sent by mail, as this was considered to be the most appropriate way to perform the lifestyle intervention in participants living disseminated over the country and recruited during a 3-year period. The feasibility of telephone-based and mail-based approaches to modify lifestyle in women with breast cancer has already been demonstrated in other lifestyle intervention studies.[12 27–29]

There is broad agreement that randomised controlled trials with large sample sizes are needed to study the effects of comprehensive lifestyle intervention programmes on cancer prognosis in breast cancer survivors. The SUCCESS C Study is one of only a few such studies. Another ongoing large-scale lifestyle intervention study is the Diana-5 (Diet and Androgens) Trial which is examining the effectiveness of a Mediterranean-macrobiotic diet in women with early stage invasive breast cancer.[30] Finally, the Alliance A011401 project tries to evaluate the effect of weight loss in the adjuvant treatment of overweight and obese women with breast cancer.[31]

It is expected that the lifestyle intervention may show beneficial effects on other diseases beyond the hypothesised effect on breast cancer survival. Thus, as breast cancer is becoming a chronic disease,[32] and patients are at risk of developing a variety of other lifestyle-associated diseases including type 2 diabetes or cardiovascular disease, their prognosis may be strongly influenced by such diseases.[33] It is also noteworthy that metabolic disturbances may act as a common soil for both breast cancer and cardiovascular disease.[34] Therefore, adopting a healthy lifestyle may confer additional benefit for health and life expectancy in women with breast cancer.

CONCLUSION

The lifestyle intervention part of the SUCCESS C Study addresses the important, but still unanswered question if a long-term modification of lifestyle in women with breast cancer may have a positive impact on disease-free survival. The study will also provide robust data on the efficacy and safety of a weight loss and comprehensive lifestyle modification programme in these patients.

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Contributors WJ designed the SUCCESS C Trial. DH, BR and HH developed the lifestyle part of the SUCCESS C Trial. DH supervised the lifestyle coaching. TF is responsible for statistics. BR and PH were responsible for supervision and support of the study centers. DH and HH were mainly responsible for the preparation of the manuscript. BR, TF, PH and WJ reviewed and commented on the manuscript.

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