Changes in body composition as a result of chemotherapy

Comparing women with and without breast cancer

Maaike M.G.A. van den Berg

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Thesis committee

Promotors
Prof. Dr E. Kampman
Professor of Nutrition and Disease
Wageningen University & Research

Prof. Dr M. Visser
Professor of Healthy Aging
VU University Amsterdam
EMGO Institute Amsterdam

Co-promotors
Dr R.M. Winkels
Research associate
Penn State Hershey, Cancer Institute, USA

Dr J.H.M. de Vries
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Wageningen University & Research

Other members
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Dr A.M. May, UMC Utrecht, Utrecht

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Maaike M.G.A. van den Berg

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Maaike M.G.A. van den Berg

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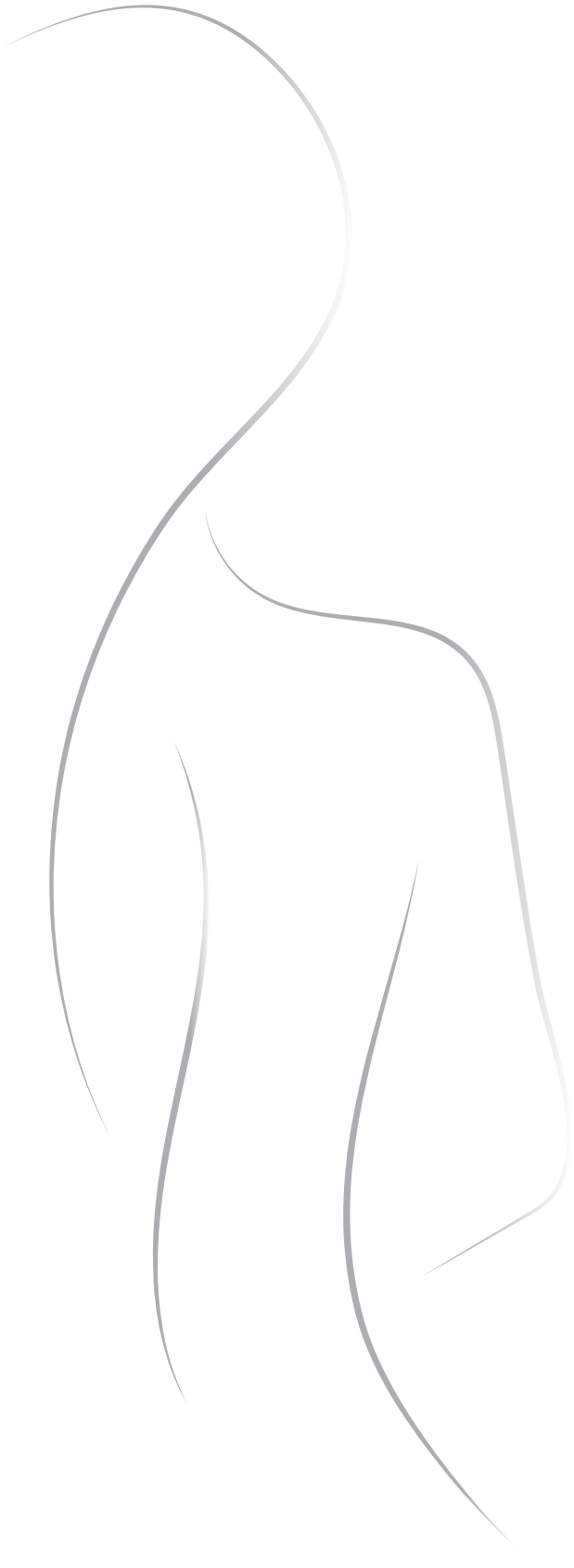
Table of Contents



Chapter 1

General introduction

Breast cancer is the most diagnosed type of cancer in women worldwide, with an incidence of nearly 1.7 million new cases diagnosed in 2012[1]. Breast cancer represents approximately 12% of all new cancer cases and 25% of all cancers in women[1]. In the Netherlands, the incidence of breast cancer has increased over the years, while mortality has decreased. In 2014, 14.556 women were diagnosed with invasive breast cancer, while 3.041 women died because of breast cancer in the same year[2]. Because of screening and improvements in treatment options, the 5-year overall survival rate of breast cancer in the Netherlands increased from 77% for patients diagnosed between 1989 and 1993 to 87% for patients diagnosed between 2008 and 2012 (figure 1.1)[2-4].

Breast cancer overall suvival rate in The Netherlands

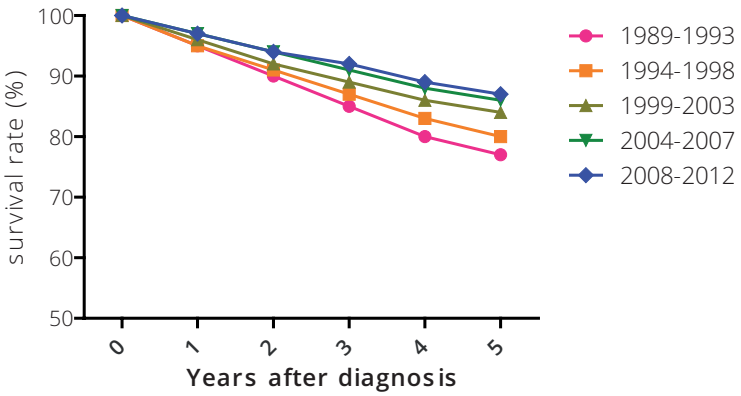


Figure 1.1. The overall survival rate for breast cancer patients in the Netherlands for different periods of diagnosis based on data from the Dutch cancer registry[2]

Treatment for early stage breast cancer consists of surgery, mostly in combination with radiotherapy, chemotherapy, endocrine therapy, targeted and/or immunotherapy. Chemotherapy regimens changed from cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in the 1970s and 1980s, to anthracyclines in the 1990s, to combination regimes including taxanes in the 2000s[5-7]. Currently, chemotherapy for breast cancer mostly consists of third generation schemes which combine anthracyclines (e.g. doxorubicin, epirubicin) and taxanes (e.g. paclitaxel, docetaxel) with or without trastuzumab. In the Dutch cancer clinical practice

guidelines, the type of chemotherapy recommended depends on several factors, such as age, size of tumour, involved lymph nodes and HER-2 status[8]. Table 1.1 gives an overview of the currently recommended chemotherapy regimens for early breast cancer in the Netherlands by HER-2 status[8].

Table 1.1. Currently recommended chemotherapy treatment regimens for early stage breast cancer in the Netherlands[8]

HER-2 status	Regime	Scheme of treatment
HER-2 negative	TAC	6 times docetaxel, doxorubicin and cyclophosphamide every 3 weeks
	FEC/DOC	3 times fluorouracil, epirubicin and cyclophosphamide every 3 weeks, followed by 3 times docetaxel every 3 weeks
	AC/P(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 12 times paclitaxel
	AC/DOC/(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 4 times docetaxel
HER-2 positive	AC/P(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 12 times paclitaxel with trastuzumab every week
	AC/DOC/(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 4 times docetaxel with trastuzumab every 3 weeks

Because of the improved survival rate, short and long term adverse effects of treatment have become increasingly important. Body weight and body composition before, during and after chemotherapy may affect side effects during treatment and survival. In the next paragraphs this will be discussed further.

Body weight and body composition at diagnosis

High BMI or obesity before diagnosis of breast cancer is consistently associated with increased risk of overall and breast cancer specific mortality in meta-analyses[9-12]. Knowledge of the association between pre-diagnosis body composition and survival is limited. Several studies suggest that a higher waist-hip ratio is associated with an increased risk of breast cancer mortality, although results are inconsistent[13-18].

Body weight and body composition have not only been associated with survival; studies in other types of cancer suggest that pre-diagnosis body composition may also affect the risk of chemotherapy-induced toxicity. Severe toxicities during chemotherapy may lead to a postponement of treatment, dose reduction or a premature termination of the treatment. These changes in treatment eventually may lead to a lower total administered dose, and worse outcome[19]. Studies of other cancer types have shown that chemotherapy-induced toxicity is highest in patients with a low lean body mass[20-25].

In metastatic breast cancer, patients with sarcopenia, low muscle mass, or low lean body mass are at an increased risk of dose limiting toxicity during chemotherapy. Body composition of patients with metastatic disease may be affected by disease-related sarcopenia and/or cachexia. Therefore it is unclear whether findings in metastatic breast cancer are generalizable to early stage breast cancer. One of the aims of this thesis was to assess the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy in early stage breast cancer patients.

Changes in body weight and body composition during chemotherapy

Several narrative reviews report weight gain in women with breast cancer during chemotherapy[26-32]. Mid-1990s reviews of the literature suggest that significant weight gain occurred in 50-96% of the breast cancer patients who received chemotherapy. Weight gain was reported to vary from 2.5 to 6.2kg, while gains of more than 10 kg were not unusual[27,28,33]. More recent studies report a lower prevalence of weight gain (35-85%), with weight gain varying between 1.4 and 5.0 kg[34-39].

There are important methodological differences between the studies published so far, which makes it difficult to compare results. These differences include the type of chemotherapy treatment, characteristics of the study participants, timing of the measurements of body weight, and the study design. As no meta-analyses among changes in body weight during chemotherapy are currently available, this thesis includes a meta-analysis on changes in body weight during

chemotherapy, taking variables which may explain heterogeneity between studies into account.

Weight gain during chemotherapy is associated with worse quality of life and self-esteem[30,31]. In addition, several studies have reported that weight gain may be associated with an increased risk of disease recurrence and poorer prognosis, however, these results are inconsistent[30,31,40-44]. A recent meta-analysis concluded that a weight gain of 10% or more after diagnosis of breast cancer is associated with higher all-cause mortality, although mainly due to one study[45]. These results suggest the importance of further investigation of weight changes during chemotherapy.

Potentially unfavourable changes in body composition may also occur during chemotherapy. Changes observed consist of an increase in fat mass with a loss or no change in lean body mass, sometimes even without weight gain[29-32]. Previous studies of changes in body composition were hampered by a small size and lack of a comparison group of women without breast cancer. Without a comparison group it is impossible to assess whether changes in body composition in breast cancer patients during chemotherapy are indeed treatment related or regular age-related changes. One of the aims of this thesis was therefore to obtain more insight in changes in body weight and body composition during chemotherapy in women with early stage breast cancer.

Determinants associated with changes in body weight and body composition during treatment

To date, it is not clear which determinants underlie the changes in body weight and body composition during chemotherapy in breast cancer patients. Several possible determinants have been described, such as treatment-induced ovarian failure accompanied by the rapid onset of menopause[46], menopausal status at diagnosis[30,31,47,48], age at diagnosis[30,39,49,] BMI, fat mass and body weight before start of chemotherapy[30,50,51], and resting energy expenditure[27,36,37,52]. In addition, several studies described reductions in physical activity during and after treatment[26,31,37,49,53].

Previous studies which investigated whether dietary intake changed during chemotherapy in

breast cancer patients produced inconsistent results. These results either showed increases[54], decreases[27,55] or no changes[26,36,52] in energy intake during chemotherapy, possibly because different studies used different methods and different time points during the course of chemotherapy to assess energy intake. Therefore we aimed to assess differences in dietary intake during chemotherapy between women with breast cancer and a comparison group of women without cancer.

Besides the meta-analysis of previous studies, we conducted an observational study among breast cancer patients stage I-IIIB and among an age-matched comparison group of women without cancer to assess changes in body weight and body composition during chemotherapy, named the COBRA-study (Change Of Body composition in Breast cancer: All-in assessment).

The COBRA-study

The COBRA-study is a prospective study of newly diagnosed, operable, stage I-IIIB breast cancer patients scheduled for chemotherapy and a comparison group of women without diagnosed cancer of a similar age (range +/- 2 years). Patients were followed from before chemotherapy until a half year after chemotherapy. Women in the comparison group were followed until a year after inclusion. Eligible patients were recruited by the staff of 11 participating hospitals in the Netherlands prior to commencement of chemotherapy. Participants in the comparison group were recruited via patients, who were asked to distribute envelopes with study information to friends, acquaintances and colleagues. Women without cancer interested in participating in the study could contact the researchers. All study participants needed to be at least 18 years old and able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, pregnancy or the intention to get pregnant during the study period, dementia or other mental conditions that made it impossible to comply with the study procedures. The study design consist of different moments of measurement, see figure 1.2.

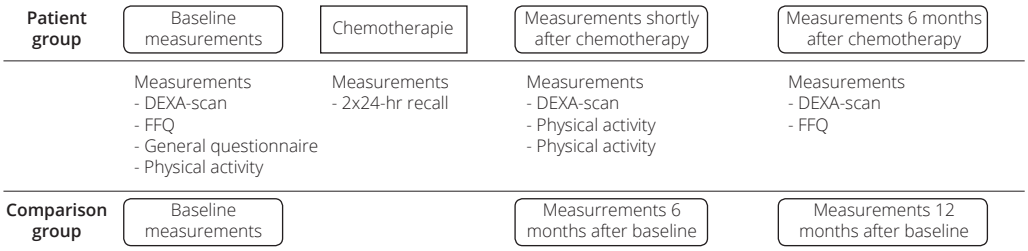


Figure 1.2. Study design of the COBRA-study

Aim and outline of this thesis

The aims of this thesis are, to assess among patients with stage I-IIIB breast cancer:

1. the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy.
2. potential changes in body weight and body composition during and after chemotherapy compared to changes in age-matched women without cancer in the same time period.
3. dietary intake during chemotherapy compared to age-matched women without cancer in the same time period.

Chapter 2 describes the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy in early stage breast cancer patients found within the COBRA-study. **Chapter 3** presents the results of a meta-analysis to quantify changes in body weight during chemotherapy in early stage breast cancer patients and to identify which factors contribute to the heterogeneity between studies. **Chapter 4** presents the results of the COBRA-study, investigating changes in body composition during treatment in breast cancer patients compared to women of a similar age without cancer and the determinants associated with these changes. **Chapter 5** describes the differences in dietary intake during chemotherapy treatment in breast cancer patients compared with women without cancer in the COBRA-study. In the final chapter of this thesis, **Chapter 6**, the main findings of the chapters are summarized and discussed. This chapter also includes recommendations for clinical practice and future research.

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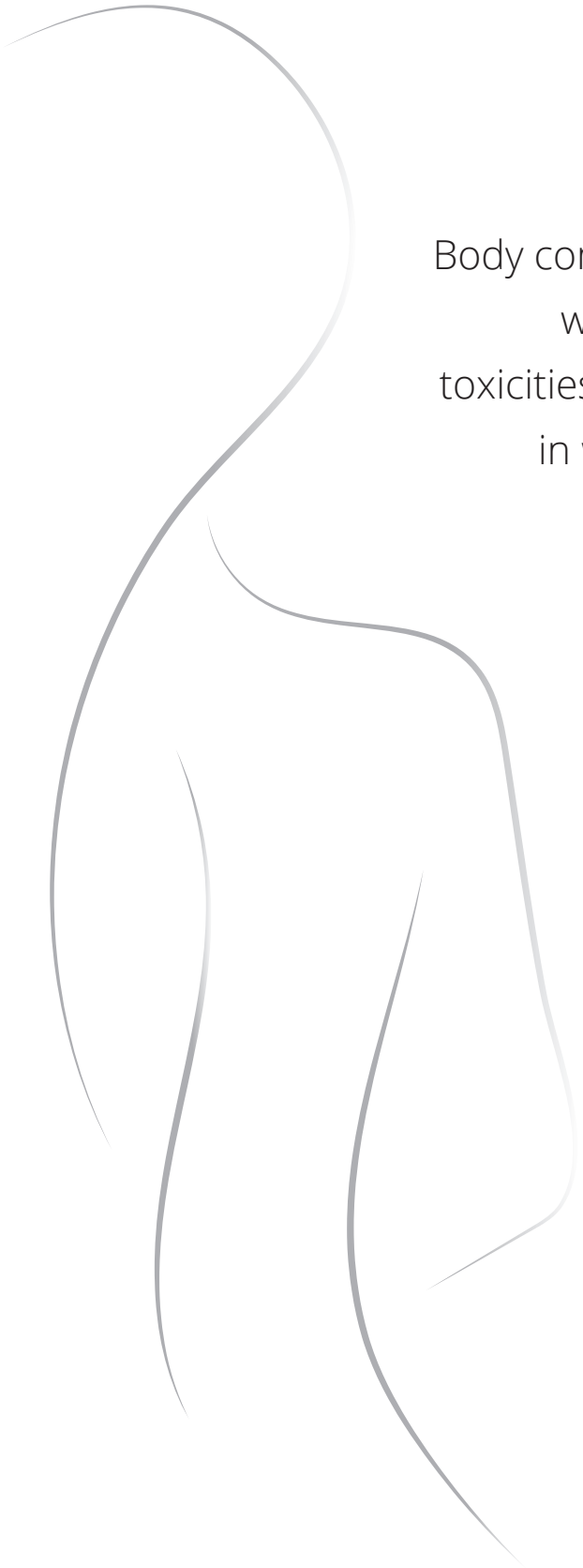

Chapter 2

Body composition is associated with risk of dose-limiting toxicities during chemotherapy in women with stage I-IIIB breast cancer

M.M.G.A. van den Berg,
D.E.G. Kok,
E.E. Posthuma,
L. Kamps,
C.S. Kelfkens,
N. Buist,
M. Geenen,
A. Haringhuizen,
J.B. Heijns,
R.H.M.A. van Lieshout,
M. Los,
D.W. Sommemeijer,
J.N.H. Timmer-Bonte,
J.Th.C.M. de Kruif,
H.W.M. van Laarhoven,
E. Kampman,
R.M. Winkels

Submitted

Abstract

Purpose: The initial dose of chemotherapy is calculated based on body surface area, which does not take body composition into account. The aim of this study was to assess the association between fat mass (kg and relative to total body weight), lean body mass (kg and relative to total body weight), and risk of dose-limiting toxicities defined as dose reductions, cycle delays or premature termination of chemotherapy in breast cancer patients.

Methods: Data were included from 172 women with breast cancer (stage I-IIIB) treated with chemotherapy. Body composition was assessed using a total body Dual-Energy X-ray Absorptiometry scan. Information regarding dose-limiting toxicities was abstracted from medical records. Prevalence ratios were calculated to assess the association between body composition and the risk of dose-limiting toxicity. All analyses were adjusted for age.

Results: 95 out of 172 patients experienced dose-limiting toxicity (55%). Higher BMI was associated with a higher risk of dose-limiting toxicity (PR 1.04 per kg/m^2; 95%CI 1.01-1.06). Similar results were found for a higher fat mass (kg and percentage) (PR: 1.08 per 5 kg; 95%CI 1.03-1.14 and PR 1.13 per 5 percent; 95%CI 1.04-1.24, respectively). Higher percentage lean body mass was associated with a lower risk of dose-limiting toxicity (PR 0.88 per 5 percent; 95%CI 0.80-0.97). There was no association between lean body mass (kg) and risk of dose-limiting toxicities.

Conclusion: A higher BMI and a higher fat mass (kg and percentage) are associated with an increased risk of dose-limiting toxicity, while lean body mass (kg) is not associated with risk of toxicities. These data suggest that total fat mass more strongly determine the risk of dose-limiting toxicities during chemotherapy in breast cancer patients. Future studies are needed to confirm these results of an association of fat mass with dose-limiting toxicities during chemotherapy.

Introduction

Breast cancer patients are often treated with chemotherapy, which usually consist of a combination of anthracyclines (e.g. doxorubicin, epirubicin) and taxanes (e.g. paclitaxel, docetaxel) with or without targeted therapy[1]. Severe side effects during chemotherapy can lead to a dose reduction, cycle delay, or premature termination of treatment, commonly referred to as dose-limiting toxicity, which eventually may lead to a reduced dose intensity, and worse outcome[2].

In clinical practice, the administered dose of the chemotherapy is based on the body surface area (BSA). BSA is usually calculated using the Mosteller formula based on height and weight[3]; it does not distinguish lean body mass from fat mass or other characteristics of body composition. It has been suggested that body composition may be more important than body surface area for calculating the administered dose of chemotherapy, since previous studies in other cancer types showed that patients with low lean body mass have a higher risk of a dose limiting toxicity[4-9].

In metastatic breast cancer, patients with sarcopenia or low muscle mass or low lean body mass are at an increased risk of dose-limiting toxicity during chemotherapy[10-12]. Body composition of metastatic breast cancer patients generally differs from early stage breast cancer patients, because of disease related sarcopenia and/or cachexia. Therefore, findings in metastatic breast cancer may not be generalizable to early stage breast cancer[10,12,13].

So far, only two studies focused on treatment-related toxicities in early stage breast cancer patients were published. These studies showed that a lower lean body mass was associated with an increased risk of toxicities[14,15].

The aim of this paper was to assess the association between fat mass, lean body mass, and the risk of a dose-limiting toxicity in women with breast cancer stage I-IIIB receiving neo-adjuvant chemotherapy.

Materials and Methods

Participants

This study is part of the COBRA-study, an observational multi-centre study among breast cancer patients receiving neo-adjuvant chemotherapy[16]. Eligible patients were recruited by the medical staff from 11 academic and peripheral hospitals in the Netherlands prior to commencement of chemotherapy. Women were eligible if they were newly diagnosed with operable stage I-IIIB breast cancer, and scheduled for 2nd or 3rd generation neo-adjuvant chemotherapy. Participants needed to be at least 18 years old and be able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, (intended) pregnancy during the study period, dementia or other mental conditions that made it impossible to comply with the study procedures.

For the current analyses, data were available for 176 breast cancer patients of the COBRA-study recruited between May 2013 and September 2016. Four patients had to be excluded, because they had no Dual-Energy X-ray Absorptiometry (DEXA)-scan available. In total we considered 172 participants for the analyses for this study.

The study protocol was approved by the Medical Ethical Committee of Wageningen University, the Netherlands. All participants provided written informed consent before enrolment.

Data collection

Body composition

Body composition was assessed using a DEXA-scan. Participants were measured in the hospitals by trained technicians using a total body scan protocol prior to start of chemotherapy (n=86) or during the first cycle of chemotherapy (n=86). Based on the total body DEXA-scan body weight (kg), fat mass (kg and relative to total body weight), and lean body mass (kg and relative to total body weight) were assessed.

Treatment-related toxicity

Information regarding chemotherapy and toxicity was abstracted from medical records using a standardized form. Treatment information included detailed information on type and dose

of chemotherapy, number of cycles planned, and start dates of each cycle. Furthermore, information on actual administered dose, toxicities and reasons for a dose-limiting toxicity were collected per cycle. Dose-limiting toxicities were defined as dose reductions, cycle delays or premature termination of chemotherapy. Also, if a planned cytotoxic regime was changed to another regime because of toxicities, this was reported as a dose-limiting toxicity. If the reason for a dose reduction or cycle delay was unknown (n=4) we included them as dose-limiting toxicity. Logistical or other non-medical reasons for cycle delays were not classified as a dose-limiting toxicity.

Patient and clinical characteristics

Information about tumour stage at diagnosis and timing of chemotherapy (adjuvant versus neo-adjuvant) was collected from medical records. Information regarding age at cancer diagnosis and height were collected using a general questionnaire. Based on body weight of the DEXA-scan and self-reported height, BMI at diagnosis was calculated. Chemotherapy regimens were categorized as combined and sequential regimes (supplementary table 2.1); combined regimes included schemes with different components administered together during all cycles, and included TAC, FEC, DOC-CYCLO, CDT(P) PT, and CTP. Sequential regimes included schemes with different components that were administered in different cycles and included AC/P(T), FEC/DOC, and AC/DOC/(T).

Data analysis

Population characteristics are presented as median with interquartile range (IQR) or number with percentage for the total study population, and participants experiencing a dose-limiting toxicity (yes versus no) separately.

Prevalence ratios (PRs) including 95% confidence intervals (CI) were calculated to assess the association between body composition and the occurrence of dose-limiting toxicity (yes versus no) using a Cox proportional hazard regression model with a fixed time[17]. For all analyses separate models were built for each body composition parameter, i.e. BMI (kg/m^2), fat mass per 5 percent, fat mass per 5 kg, lean body mass per 5 percent, and lean body mass per 5 kg.

Stratified analyses were conducted for patients receiving a sequential regime versus a combined regime, and for patients receiving adjuvant chemotherapy versus neo-adjuvant chemotherapy.

A sensitivity analysis was conducted for dose-limiting toxicities occurring within the first 6 cycles of chemotherapy. This was done to account for the fact that patients with a higher number of cycles planned have higher odds of experiencing toxicities as they go through more cycles. In this sensitivity analysis, only dose-limiting toxicities occurring within the first 6 cycles were considered.

Analyses were adjusted for age, since older women have an increased risk of experiencing toxicities and age is associated with specific body composition characteristics[18]. Based on literature, BSA was considered as potential covariate, but not included in the analyses since BSA was strongly related with the body composition parameters (multicolinearity). All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Patient characteristics

The median age of the 172 women included was 51.8 years (table 2.1). More than half of the participants were overweight or obese at diagnosis. Most patients had a stage II tumour, received adjuvant chemotherapy with a sequential regime consisting of 6 or less planned cycles. Table 1 shows that women experiencing a dose-limiting toxicity were more often treated with a sequential regime of adjuvant chemotherapy compared to the women not experiencing a dose-limiting toxicity. In addition, women experiencing a dose-limiting toxicity had a higher body weight, were more often overweight or obese, had a higher fat mass and lower percentage of lean body mass compared to the women not experiencing a dose-limiting toxicity.

Frequency of first dose-limiting toxicities

Table 2.2 shows the frequency of first dose-limiting toxicities. During chemotherapy, more than half of the patients experienced a dose-limiting toxicity (95 out of 172 patients, 55%). Of these

95 patients, 14% (n=13) stopped prematurely, 53% (n=50) had a dose reduction and 34% (n=32) had a cycle delay as their first dose-limiting toxicity. In total, 48% (n=57) of the women receiving 6 or less planned cycles experienced a dose-limiting toxicity versus 72% (n=38) of the women receiving more than 6 planned cycles.

Table 2.1. Demographic and clinical characteristics of the patient group included in the study.ble 2.2.

Characteristics	**Total (n=172)**	**Dose-limiting toxicity yes (n=95)**	**Dose-limiting toxicity no (n=77)**
Demographics			
Age, years (median, IQR)	51.8 (46.8 ; 59.1)	52.1 (47.4 ; 60.8)	51.5 (46.4 ; 54.6)
Medical profile			
Stage (n, %)			
I	44 (25.6)	26 (27.4)	18 (23.4)
II	105 (61.1)	57 (60.0)	48 (62.3)
III	23 (13.4)	12 (12.6)	11 (14.3)
Chemotherapy (n, %)			
Adjuvant	111 (64.5)	67 (70.5)	44 (57.1)
Neo-adjuvant	61 (35.5)	28 (29.5)	33 (42.9)
Type of chemotherapy (n, %)			
Combined regime	78 (45.3)	36 (37.9)	42 (54.6)
Sequential regime	94 (54.7)	59 (62.1)	35 (45.5)
Number of cycles chemotherapy (n, %)			
6 or less	119 (69.2)	57 (60.0)	62 (80.5)
More than 6	53 (30.8)	38 (40.0)	15 (19.5)
Body composition			
Body weight, kg (median, IQR)	70.5 (63.9 ; 81.7)	74.1 (64.4 ; 84.6)	68.2 (63.1 ; 76.1)
Body height, cm (median, IQR)	168 (164 ; 173)	168 (162 ; 173)	168 (164 ; 173)
Body surface area (BSA), (median, IQR)	1.8 (1.7 ; 2.0)	1.8 (1.7 ; 2.0)	1.8 (1.7 ; 1.9)
Body Mass Index (BMI) kg/m^2 (median, IQR)	25.5 (22.5 ; 29.1)	26.5 (23.9 ; 29.8)	24.5 (21.7 ; 27.2)
Fat mass, percentage (median, IQR)	36.7 (31.4 ; 42.2)	38.6 (33.7 ; 44.8)	35.0 (29.7 ; 39.9)
Fat mass, kg (median, IQR)	26.0 (20.2 ; 34.2)	27.6 (20.8 ; 36.3)	23.1 (18.4 ; 31.1)
Lean body mass, percentage (median, IQR)	60.2 (33.2 ; 65.1)	58.5 (53.1 ; 63.5)	61.8 (57.2 ; 66.7)
Lean body mass, kg (median, IQR)	43.1 (29.4 ; 46.8)	43.1 (39.5 ; 47.5)	42.8 (39.3 ; 46.6)
Appendicular skeletal mass, kg (median, IQR)	18.2 (16.8 ; 20.2)	18.2 (16.6 ; 20.2)	18.2 (16.9 ; 20.1)
Skeletal muscle index, kg/m^2 (median, IQR)	6.5 (6.0 ; 7.2)	6.5 (6.0 ; 7.3)	6.4 (6.0 ; 7.1)

Abbreviations; IQR Interquartile range; 95% CI 95% confidence interval; BMI body mass index;

Table 2.2.Frequencies of first dose limiting toxicities experienced by patients.

Toxicity	All patients (n=172)	6 planned cycles or less (n=119)	More than 6 planned cycles (n=61)
Any dose-limiting toxicity	95 (55.2)	57 (47.9)	38 (71.7)
Cycle delay	32 (33.7)	17 (29.8)	15 (39.5)
Dose reduction	50 (52.6)	36 (63.2)	14 (36.8)
Premature termination	13 (13.7)	4 (7.0)	9 (23.7)

Results are presented for all patients and stratified by number of cycles. Presented as number and percentage.

BMI and body composition and risk of dose-limiting toxicity

A higher BMI was associated with a higher risk of a dose-limiting toxicity (PR 1.04 per kg/m^2; 95%CI 1.01-1.06) as was a higher fat mass and fat percentage (PR: 1.08 per 5 kg; 95%CI 1.03-1.14 and PR 1.13 per 5 percent; 95%CI 1.04-1.24, respectively), see table 2.3. A higher percentage of lean body mass was associated with a lower risk of a dose-limiting toxicity (PR 0.88 per 5 percent; 95%CI 0.80-0.97). The body composition indicator lean body mass in kg was not associated with dose limiting toxicity (table 2.3).

Sensitivity and stratified analyses

Figure 2.1 shows the time in cycle numbers until the occurrence of the first dose-limiting toxicity. In total, 73 of the 95 women (77%) experienced their first dose-limiting toxicity within the first 6 cycles of chemotherapy. Sensitivity analyses including only dose-limiting toxicities occurring within the first 6 cycles showed similar results compared to the analysis in which we included dose-limiting toxicities in all cycles (table 2.3).

Stratified results did not suggest that the associations between body composition and dose-limiting toxicity was different for combined versus sequential regimes, nor for neo-adjuvant versus adjuvant chemotherapy (data not shown).

Table 2.3. Association between body composition parameters and occurrence of any dose-limiting toxicity or time to first dose-limiting toxicity for all included patients and results of the sensitivity within the first 6 cycles of chemotherapy. Presented as prevalence or hazard ratios adjusted for age.

All included participants			
	Total/cases	**Occurrence of a dose-limiting toxicity**	
Variable		**PR**	**95% CI**
BMI per kg/m^2 *	172/95	1.04	1.01 ; 1.06
Fat mass per 5 percent*	172/95	1.13	1.04 ; 1.24
Fat mass per 5 kg*	172/95	1.08	1.03 ; 1.14
Lean mass per 5 percent*	172/95	0.88	0.80 ; 0.97
Lean mass per 5 kg	172/95	1.05	0.95 ; 1.17
Appendicular skeletal mass per kg	172/95	1.01	0.96 ; 1.06
Skeletal muscle Index per kg/m^2	172/95	1.06	0.91 ; 1.23
Sensitivity analyses			
	Total/cases	**Occurrence of a dose-limiting toxicity**	
Variable		**PR**	**95% CI**
BMI per kg/m^{2*}	172/73	1.04	1.01 ; 1.07
Fat mass per 5 percent*	172/73	1.14	1.01 ; 1.28
Fat mass per 5 kg*	172/73	1.09	1.02 ; 1.17
Lean mass per 5 percent*	172/73	0.88	0.77 ; 1.00
Lean mass per 5 kg	172/73	1.07	0.94 ; 1.22
Appendicular skeletal mass per kg	172/73	1.02	0.97 ; 1.08
Skeletal muscle index per kg/m^2	172/73	1.11	0.92 ; 1.33

Abbreviations; PR prevalence ratio; CI 95% confidence interval; BMI body mass index;
* p <0.05

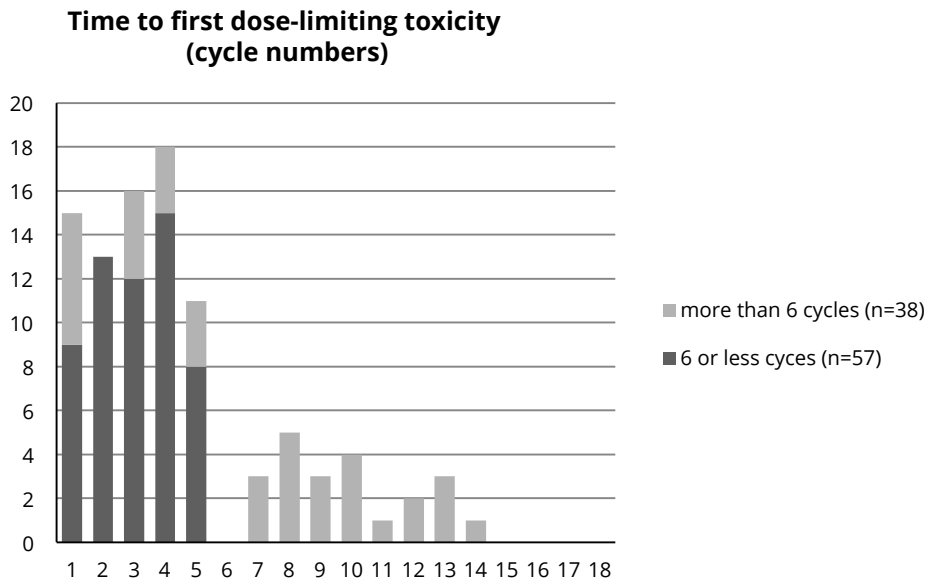

Figure 2.1. Time to first dose-limiting toxicity in cycle numbers, stratified for patients receiving a cytotoxic scheme consisting of 6 or less cycles and patients receiving a cytotoxic scheme consisting of more than 6 cycles.

Discussion

This study shows that a higher total fat mass in kg and percentage, and a lower percentage of lean body mass were associated with an increased risk of dose-limiting toxicity in breast cancer patients stage I-IIIB treated with chemotherapy, while lean body mass in kg was not associated with dose-limiting toxicities. Our results suggest fat mass strongly determine the risk of dose-limiting toxicities during chemotherapy in breast cancer patients.

In contrast, two earlier studies[14,15] stressed the importance of total lean body mass in the association with chemotherapy-induced toxicities. However, these studies did not assess chemotherapy-induced toxicities in association with relative lean body mass or total fat mass (kg or percentage). The first study (n=151) used CT-scans to assess body composition and concluded that lower total lean body mass and skeletal muscle gauge – a composite endpoint of muscle mass and muscle radio density - were associated with increased risk of treatment-related grade 3-4 toxicities in patients receiving doxorubicin-cyclophosphamide (AC)-taxane based cytotoxic regimens[14]. The second study (n=24) concluded that a lower total lean body mass was associated with higher incidence of dose-limiting toxicities during the first cycle of FEC100[15], again with CT-scan as measurement of body composition. Both studies extrapolated total lean body mass from skeletal muscle cross-sectional area of a CT-scan at the level of the third vertebrae, but did not report results of toxicity associations with percentage of total lean body mass or fat mass. Moreover, the study populations of both studies differed from our population, making it challenging to compare the results. For example, in the study of Prado 22 out of 24 patients experienced a dose-limiting toxicity during the first cycle of chemotherapy[15], which is considerably more than our study where 15 out of 172 patients had a toxicity during the first cycle. This suggests that the selection process of participants eligible for their study led to a group patients at high risk of toxicities which may impact the generalizability of those findings. In the study by Sachar et al, the average of BMI was 2 to 3 kg/m^2 higher than in our study, while lean body mass was slightly lower[14]. Baseline differences in body composition between studies plus a different outcome measure to assess toxicities obstruct direct comparison between studies.

Possible mechanisms for the observed association between body composition and chemotherapy-

induced toxicities are unclear, but could be either biological or clinical. Depending on the type of cytotoxic agent, drugs may be more hydrophilic or hydrophobic which will affect the clearance and volume of distribution of the drugs. For hydrophilic drugs, it has been hypothesized that patients with a relatively lower lean body mass may be overdosed when using body surface area to calculate dosage, and may present with higher rates of dose-limiting toxicities. In our study, it was not possible to stratify on type of chemotherapy, because of power. However, stratified results did not suggest that associations between body composition and dose-limiting toxicity were different for combined versus sequential regimes.

A more clinical, although speculative explanation for a higher risk of toxicities in patients with low lean body mass could be that clinicians treat patient with a lower percentage of lean body mass differently than patients with a higher percentage lean body mass, although this is not formally assessed. Patients with a low lean body mass may be frailer, and may generally experience other comorbidities, which could prompt the medical oncologist to adapt the chemotherapy protocol earlier than patients with a better physical condition.

In conclusion, a higher BMI and a higher fat mass (kg and percentage) are associated with an increased risk of dose-limiting toxicity, while lean body mass (kg) was not associated with risk of toxicities. This suggest that total fat mass more strongly determine the risk of dose-limiting toxicities during chemotherapy in breast cancer patients. Future studies are needed to confirm these results of an association of fat mass with dose-limiting toxicities during chemotherapy.

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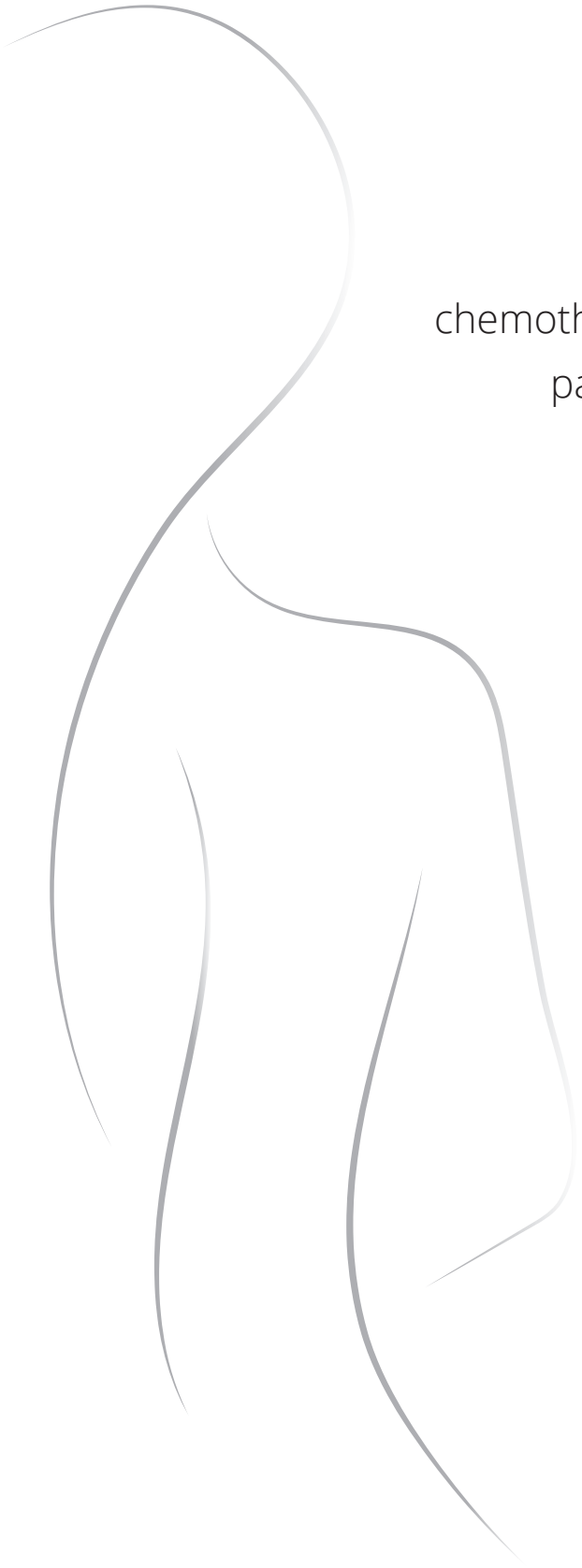
Supplementary table 2.1. Chemotherapy schemes included in the study

	Chemotherapy	**Scheme**
Combined regimens	TAC	6 times docetaxel, doxorubicin and cyclophosphamide every 3 weeks
	FEC	6 times fluorouracil, epirubicin and cyclophosphamide every 3 weeks
	DOC-CYCLO	6 times docetaxel and cyclophosphamide every 3 weeks
	CDT(P)	6 times carboplatin, docetaxel and trastuzumab with or without pertuzumab every 3 weeks
	PT	12 times paclitaxel and trastuzumab every week
	CTP	18 times carboplatin, paclitaxel and trastuzumab, every week
Sequential regimes	AC/P(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 12 times paclitaxel with or without trastuzumab every week
	FEC/DOC	times fluorouracil, epirubicin and cyclophosphamide every 3 weeks, followed by 3 times docetaxel every 3 weeks
	AC/DOC/(T)	4 times doxorubicin and cyclophosphamide every 3 weeks followed by 4 times docetaxel with or without trastuzumab every 3 weeks



Chapter 3

Weight change during chemotherapy in breast cancer patients: A meta-analysis

M.M.G.A. van den Berg,
R.M. Winkels,
J.Th.C.M. de Kruif,
H.W.M. van Laarhoven,
M. Visser,
J.H.M. de Vries,
Y.C. de Vries,
E.Kampman

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Abstract

Background: Weight gain during chemotherapy in women with breast cancer is commonly reported. However, there are important differences between studies that examined weight change during chemotherapy; e.g. type of chemotherapy, menopausal status, time between body weight measurements and sample size. The purpose of this meta-analysis was to quantify changes in body weight during chemotherapy for women with breast cancer, taking these differences into account.

Method and materials: We identified relevant studies using PubMed, Scopus and Embase databases. The search was limited to human studies published in English up to and including December 2015. Only studies among women with early stage breast cancer treated with chemotherapy, with reported body weight before and after chemotherapy and type of chemotherapy were included. Random-effect models were used, and heterogeneity between studies was explored through stratified analyses and meta-regression. Sensitivity analyses were done to explore whether a specific study markedly affected the results.

Results: In total 25 papers were found, including data from 2620 women. Overall, body weight increased during chemotherapy: 2.7kg (95% CI 2.0, 7.5) with a high degree of heterogeneity (I^2= 94.2%). Stratified analyses showed weight gain in all strata, but did not substantially reduce heterogeneity. Univariate meta-regression showed less weight gain in prospective studies compared to chart review studies (-2.0, 95%CI: -3.1, -0.8). Studies including cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimes showed a greater weight gain compared to those that did not (2.2, 95%CI: 1.1, 3.3); and papers published until the year 2000 showed a greater weight gain compared to those published after 2000 (1.9, 95%CI:-0.8, 3.1). In the multivariate models only studies including CMF regimes and studies published until 2000 were associated with significant weight gain of respectively 1.3 and 1.4kg.

Conclusion: Despite the high heterogeneity, this meta-analysis shows significant weight gain during chemotherapy for women with breast cancer. Weight gain was more pronounced in papers published until 2000 and women receiving CMF as chemotherapy regime. Although weight gain after chemotherapy has decreased over the course of time, weight gain is still substantial and deserves clinical attention.

Introduction

Treatment for early stage breast cancer mostly consists of a combination of surgery, radiotherapy, chemotherapy and hormonal therapy. Chemotherapy can cause various side effects, such as nausea, vomiting, hair loss, fatigue, mucositis, cytopenia, ovarian failure and cardiac toxicity. In addition, numerous studies have described weight gain in women with breast cancer during chemotherapy[1-8].

Several reviews reported body weight gain during chemotherapy for breast cancer patients[9-15]. Weight gain during chemotherapy was first reported in 1978 by Dixon et al[16]. Mid-1990s reviews of the literature suggest that significant weight gain occurred in 50-96% of the breast cancer patients who received chemotherapy. Weight gain was reported to vary from 2.5 to 6.2 kg, while gains of more than 10kg were not unusual[13,14,17]. More recent studies report a lower prevalence of weight gain (35-85%), with weight gain varying between 1.4 to 5.0 kg[6-8,18-20].

Body weight gain during chemotherapy treatment for breast cancer is undesirable, since it has negative influences on quality of life and health. Weight gain during treatment is associated with a negative affect on quality of life and self-esteem. In addition, several studies reported an increased risk of disease recurrence and poorer prognosis, however, these results are inconsistent[10,15,21-25]. A recent meta-analysis concluded that a weight gain of 10% or more after diagnosis of breast cancer is associated with higher all-cause mortality, mainly attributable to 1 study[26].

There are important differences between studies that examined weight change during chemotherapy in breast cancer patients, which may partly explain the large variation in body weight changes observed between studies. First, the amount and type of chemotherapy changed over time, from cyclophosphamide, methotrexate and 5-fluorouracil (CMF) in the 1970s and 1980s, to anthracyclines in the 1990s, to more taxane-based regimens nowadays[27-29]. Second, characteristics of included patients differed between studies. Some studies investigated only premenopausal women, while other studies included both, pre- and postmenopausal women. A third important difference is the time between the body weight measurements. Some studies followed patients only during chemotherapy with body weight measured before and shortly after

chemotherapy. Other studies followed patients for a year or even longer with varying moments of weight measurements during follow-up. Fourth, the sample size varied substantially between studies, ranging from less than 10 till more than 200 participants. A fifth important difference is the study design: some studies retrieved body weight as reported in the medical records, while other studies had a prospective design with standardized measurements of body weight before, during and after chemotherapy.

Reviews regarding body weight gain during chemotherapy for breast cancer patients were narrative reviews and did not provide summary estimates for weight change so far. Therefore, the purpose of this meta-analysis was to quantify changes in body weight during chemotherapy for women with early stage breast cancer, and to assess which factors contributed to the heterogeneity between studies.

Methods

Literature search

A comprehensive search of literature was conducted using PubMed, Scopus and Embase databases. Search term included: "body weight change" , "body weight", "breast cancer", "breast neoplasm", "breast carcinoma", "breast tumor", "breast tumour", "breast adenoma", "mamma," "chemotherapy", "chemo" and "cytostatic" (see additional file 3.1 for more details). The search was limited to human studies, published in English up to and including December 2015. In addition, references listed in papers were screened for additional papers, resulting in the inclusion of one additional paper.

Paper selection

Papers were included if they met the following criteria: early stage breast cancer patients treated with chemotherapy, type of chemotherapy reported, at least two measurements of body weight: one before and one after chemotherapy treatment. Both observational and intervention studies were included. Intervention studies were included if they included a control group receiving usual care; only the information of this usual care group was included in the meta-analysis.

One database was created and duplicate references were deleted. First, titles were screened on eligibility by two researchers (MB and RW). Secondly, abstracts were screened. If an abstract did not contain sufficient information to assess eligibility, the full-text was reviewed to assess eligibility. Communication letters, abstracts and poster of conferences were excluded.

Data extraction

From each relevant paper, information on first author, year of publication, country, study design, sample size, characteristics of study population (baseline age, baseline height, baseline menopausal status), breast cancer stage, type of chemotherapy, duration of chemotherapy, follow-up period between measurements of weight, adjuvant/neo-adjuvant chemotherapy, time points of weight assessment in relation to start and stop dates of chemotherapy, and weight or weight change (kg) with standard deviation (SD), 95% confidence interval or range were extracted and stored in a database.

Quality assessment

To assess whether studies of lesser quality could have influenced the results, two researchers (MB and RW) independently assessed the quality of the included studies using an adapted version of the Newcastle-Ottawa Scale for assessing the quality of nonrandomised studies[30]. Studies could get a maximum of 6 points, in four quality areas: 1) representativeness of the sample (information about number of people eligible and included); 2) loss to follow-up of participants (information about number lost to follow-up); 3) information about exposure (type of chemotherapy regimens); 4) assessment of the outcome (information how body weight was assessed). The rating system scores studies from 0 (low quality) to 6 points (high quality). A total score of 3 or less points was considered low quality, whereas a score of 4 or more points was considered high quality.

Statistical analysis

When no mean body weight change or SE was reported these were calculated if possible for each paper. When data on mean baseline weight and height were available we calculated the baseline mean BMI for the total group of participants using the formula: BMI= weight (kg) / height^2 (m). If

weight or weight change was reported for different types of chemotherapy or menopausal status separately, these results were included instead of the overall mean weight change. Random-effect models were used to calculate the mean and 95% confidence interval of the weight change during chemotherapy for breast cancer. Statistical heterogeneity between studies was assessed by the I^2 statistic. I^2 of 25%, 50% or 75% were interpreted as indicating low, moderate and high heterogeneity, respectively[31]. To investigate potential sources of heterogeneity, we conducted stratified analyses. These included the factors: type of chemotherapy (CMF included vs no CMF included), sample size (n=<100 vs n=>100), menopausal status (premenopausal, postmenopausal, both), baseline mean BMI (20.0-24.9 vs 25.0-29.9), study design (prospective vs chart review), second measurement of body weight (the end of chemotherapy / 6 months after baseline' group vs '6 months after chemotherapy / 12 months after baseline' group), year of publication (before and including 2000 vs after 2000), country (US, Canada, Western Europe, Australia, Turkey, Korean) and study quality (low quality vs high quality) . Of all factors included in the stratified analysis with data available of all estimates we conducted meta-regression analyses. We included the factors that were statistically significant in the univariate stratified analyses in a multivariate regression analysis. Regression coefficients, 95% confidence intervals and p values were reported. Sensitivity analyses were conducted by excluding one study at a time to explore whether one study markedly affected the results or highly contributed to the heterogeneity. A second sensitivity analysis was conducted by excluding the only intervention study included. Finally, sensitivity analyses were done excluding studies included < 50 participants, and excluding studies included >200 participants to explore whether the smallest or largest studies markedly affect the results. Statistical analyses were conducted using STATA version 11 (StataCorp, College Station, TX). A p-value < 0.05 was considered statistically significant.

Results

The results of the literature search and study selection are summarized in Figure 3.1. In total the database searches yielded 2,445 references. After duplicates were deleted 2,022 titles and 138 abstracts were screened for eligibility. A total of 52 full texts were screened, of which 27 papers were excluded, resulting in 25 eligible papers. Papers were excluded for the following

reasons: full-text could not be obtained (n=2); articles did not report a weight change (n=4); articles included a variety of cancer types and did not report results for breast cancer separately (n=3); articles did not report weight changes during chemotherapy (n=3); weight change was not reported in kg, but only as percentage change (n=4); type of chemotherapy was not reported (n=4); chemotherapy was combined with other treatment e.g. radiotherapy (n=4); only an intervention group (n=2). One paper was excluded because a more recent paper about the same study was published. In total, 34 weight change estimates from 25 papers were included in this meta-analysis. Six papers reported results for weight gain in subgroups receiving different kind of chemotherapy treatments.

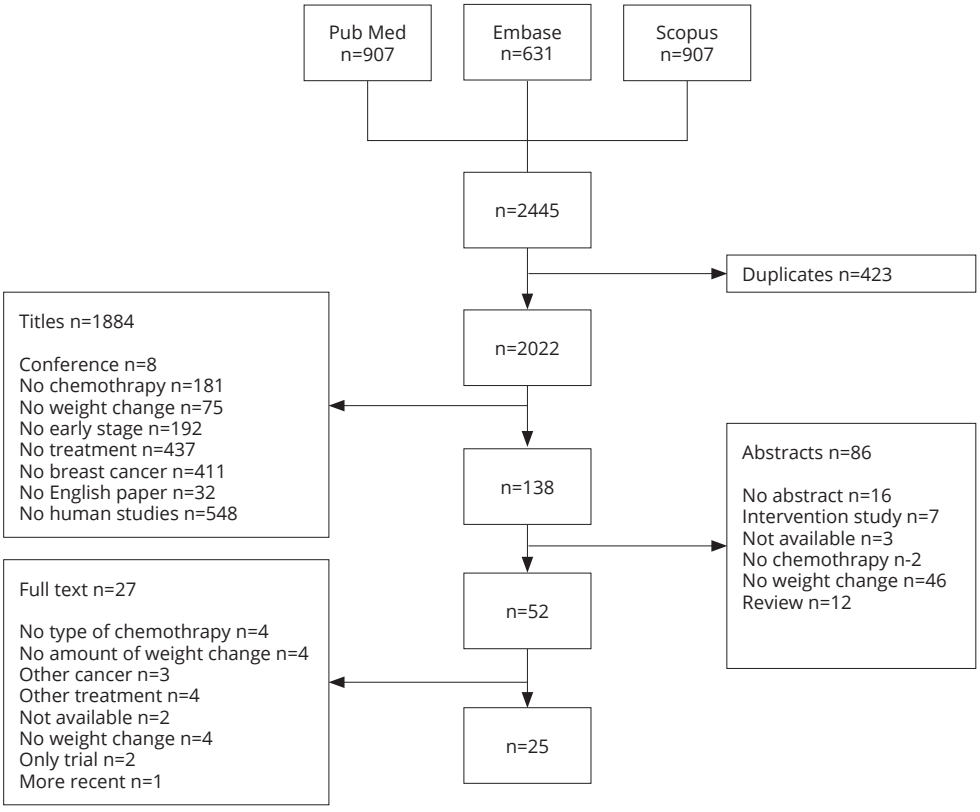

Figure 3.1. Paper screening and data extraction progress

Characteristics of the participants and study designs

Characteristics of the studies included in this meta-analysis are shown in Table 3.1. The 25 papers were published between 1985 and the end of 2015. Thirteen weight change estimates were published up to and including 2000 [17,32-38] , and 21 after 2000 [1,6-8,12,18-20,39-47]. In total, 20 weight change estimates included patients treated with CMF. Sixteen weight estimates retrieved body weight from medical chart review. Eighteen had a prospective design of which one body weight estimate was an intervention study. Sample size of the body weight estimates varied from 8 to 483 participants. All papers used body weight before start of chemotherapy as baseline measure. For the second time point of measurement we created two groups: 1) 'the end of chemotherapy / 6 months after baseline' group and 2) 'the 6 months after chemotherapy / 12 months after baseline' group. The first group contained studies for which the second measurement was either directly after chemotherapy or 6 months after diagnosis, the second group all studies for which the second measurement was 6 months after chemotherapy or 12 months after diagnosis.

Overall, data from 2620 women were included in this meta-analysis. The mean age of the study samples ranged from 39-56 years. Most papers included a combination of pre- and postmenopausal women. Seven papers included only premenopausal women. Two papers showed results separately for pre- and postmenopausal women. Table 3.2 gives an overview of the quality assessment of the studies included in this meta-analysis. 8 papers scored a total of 3 or less points for study quality and were assessed as low quality studies.

Table 3.1. Papers included in this meta-analysis of weight change during chemotherapy for women with early stage breast cancer

First author, year of publication	Year of enrolment	Study design	Sample (sample size, key characteristics)	Type of chemotherapy	Follow-up	Mean weight gain in kg (se) in total group	Subgroup analysis Mean weight gain in kg (se)
Foltz, 1985	UN	Prospective	n=34, pre- and postmenopausal, stage II, adjuvant	CMF	Pretreatment - 6 months	2.99 (2.85)	
Heasman, 1985	1975-1981	Retrospective Chart review	n=237, pre- and postmenopausal, adjuvant	n=46 single agent chemotherapy n= 112 CMF n=79 CMF + prednisone	Pre–posttreatment	4.32 (0.23)	Single agent: 2.72 (0.33) CMF: 3.65 (0.32) CMF + prednisone: 6.20 (0.4)
Huntington, 1985	UN	Retrospective Chart review	n= 29, pre- and postmenopausal, adjuvant	n=18 CMF n=11 CMFVP	Pre–posttreatment	4.58 (0.58)	Premenop: 7.67 (0.89) Postmenop: 2.63 (0.72) Perimenop: 4.76 (0.12)
Goodwin, 1988	1960-1984	Retrospective Chart review	n=193, pre- and postmenopausal, adjuvant	n=113 CMF n=80 CMF + prednison	Pretreatment - 12 months		CMF: 2.51 (0.24) CMF+ prednison 5.55 (0.62)
Demark –Wahnefried, 1997	1993-1995	Prospective	n=18, premenopausal, adjuvant	n= 9 AC n= 5 CAF n=1 CMF n=1 CMF + leucovorin n=1 A + CMF n=1 AC + leucovorin	Pre-posttreatment	0 (3.48)	
Aslani, 1999	UN	Prospective	n= 25, pre- and postmenopausal, adjuvant	CMF	Pre-posttreatment	2.35 (0.62)	
Goodwin, 1999	1989-1996	Prospective	n= 176, pre- and postmenopausal, adjuvant	n=128 non-antracyclines n=48 antracyclines	Pretreatment - 12 months	2.5 (0.36)	
Kutynec, 1999	UN	Prospective	n=8, pre- and perimenopausal, adjuvant	AC	Pre-posttreatment	0 (2.85)	
Demark-Wahnefried, 2001	1995-1999	Prospective	n=36, premenopausal, adjuvant	n= 17 doxorubicin regimens n= 12 doxorubicin regimens + tamoxifen, n= 6 CMF n= 1 CMF + tamoxifen	Pretreatment – 6 months	2.2 (0.37)	

McInnes, 2001	UN	Retrospective Chart review	n=44, pre- and postmenopausal, adjuvant	n= 19 CMF - oral n= 6 CMF - iv n= 2 CAF - oral n= 9 CAF - iv n= 8 Other	Pretreatment – 6 months	3.4 (0.33)	
Del Rio, 2002	UN	Prospective	n=30, premenopausal, adjuvant	CMF	Pretreatment – 6 months	2.8 (0.56)	
Lankester, 2002	1998	Retrospective Chart review	n=100, pre- and postmenopausal, adjuvant + neo-adjuvant	n=69 FEC n=31 CMF	Pretreatment- before last cycle	3.68 (0.4)	
Freedman, 2004	1999-2001	Prospective	n=20, pre- and posttreatment, adjuvant	n=8 AC n= 10 AC + paclitaxel n= 2 AC + docetaxel	Pre-posttreatment	-0.83 (0.81)	
Harvie, 2004	UN	Prospective	n=17, pre- and postmenopausal, adjuvant	n=12 FEC n= 5 CMF	Pre-posttreatment	3.3 (1.02)	
Ingram, 2004	UN	Prospective	n=76, premenopausal, adjuvant	n= 39 AC n= 33 CEF n= 4 CMF	Pre-posttreatment	1.4 (0.39)	AC: 1 (0.34) CEF: 1.5 (0.77) CMF: 5 (1.8)
Kunmar, 2004	UN	Prospective	n=170, pre- and postmenopausal, adjuvant	n= 107 CA n= 45 CA + taxol n= 17 other	Pre-posttreatment	0.4 (1.13)	
Campbell, 2007	2001-2003	Prospective	n=10, pre- and postmenopausal, adjuavnt	n=5 CEF n=5 AC	Pre-posttreatment	1.98 (5.06)	
Courneya, 2007	2003-2005	Trial	n=82 pre- and postmenopausal, adjuvant	n= 23 FE100C n= 20 AC n= 8 CE120F n= 3 other non-taxane n= 10 TAC n= 14 AC-taxane n= 4 other taxane	Pre-posttreatment	1.2 (1.71)	
Makari-Judson, 2007	1997-2002	Retrospective Chart review	n=123, pre- and postmenopausal, adjuvant	AC, AC + taxane, CAF, Doxorubicin + CMF, CMF or MF n=109 antracycline containing CT n=14 non antracycline	Pretreatment - 12 months	2.6 (0.57)	

Heideman, 2009	1974-2006	Retrospective Chart review	n=31 (CT only), pre- and postmenopausal, adjuvant	AC, EC, CMF, FAC, FEC, other incl herceptin	Pretreatment - 12 months	2.2 (2.07)	
Heideman, 2009	1974-2006	Retrospective Chart review	n=67 (Combined), pre- and postmenopausal, adjuvant	AC, EC, CMF, FAC, FEC, other incl herceptin	Pretreatment - 12 months	2.6 (1.69)	
Biglia, 2010	2007-2008	Prospective	n=34, premenopausal, adjuvant	n=17 FEC n=17 FEC + taxotere	After surgery-end CT	2.07 (0.45)	
Tredan, 2010	2004-2006	Prospective	n=242, pre- and postmenopausal, adjuvant	n= 110 anthracycline without taxane n= 156 anthracycline + taxanen n= 2 taxanen (1%) n= 4 missing data	Pretreatment – 6 months after CT	0.7 (0.23)	Premenopausal: 1.2 (0.31) Postmenopausal: 0.2 (0.33)
Basaran, 2011	2003-2004	Retrospective Chart review	n=171, pre- and postmenopausal, adjuvant	N=111 Antracycline based N=55 Antracycline/taxane N=5 No CT	Pre-posttreatment	1.7 (0.94)	
Jeon, 2014	2005-2010	Retrospective Chart review	N=108, pre- and postmenopausal, adjuvant	TAC	Pre-posttreatment	3.64 (3.7)	
Winkels, 2014	2001-2010	Retrospective Chart review	N=483, pre- and postmenopausal	n=289 antracycline based n=170 antracycline + taxane n=10 CMF n=14 other	Pre-posttreatment	1.2 (0.25)	

UN=unknown

Table 3.2. Summary of the quality assessment of included studies using an adapted version of the Newcastle-Ottawa scale for assessing the quality of nonrandomised studies.

First author, year of publication	Representativeness of sample (2 points)	Loss to follow-up of participants (1 point)	Information about exposure (1 point)	Measurement of outcome (2 point)s	Total score
Foltz,1985	2	1	1	1	5/6
Heasman, 1985	2	1	1	1	5/6
Huntington, 1985	1	0	1	1	3/6
Goodwin ,1988	2	1	1	1	5/6
Demark-Wahnefried, 1997	1	1	0	1	3/6
Aslani, 1999	1	1	1	1	4/6
Goodwin, 1999	1	1	0	2	4/6
Kutynec , 1999	2	1	1	1	5/6
Demark-Wahnefried, 2001	2	1	0	2	5/6
McInnes, 2001	1	1	0	1	3/6
Del Rio, 2002	1	1	1	0	3/6
Lankester, 2002	1	1	0	1	3/6
Freedman, 2004	1	1	0	2	4/6
Harvie, 2004	1	1	0	2	4/6
Ingram, 2004	2	1	1	2	6/6
Kumar, 2004	2	1	0	1	4/6
Campbell, 2007	1	1	0	2	4/6
Courneya, 2007	2	1	0	1	4/6
Makari-Judson, 2007	2	1	0	1	4/6
Heideman, 2009	2	1	0	1	4/6
Biglia, 2010	1	1	0	0	2/6
Tredan, 2010	1	1	0	1	3/6
Basaran, 2011	1	0	0	1	2/6
Jeon, 2014	1	1	1	1	4/6
Winkels, 2014	2	1	1	1	5/6

(1) Representativeness of sample (2 points: extensive information on number of people eligible and included, 1 point: extensive information about recruitment, but not about number of people eligible and included, 0 points: only brief information about recruitment.
(2) Loss to follow-up of participants (1 point: information about number lost to follow-up; 0 points: no information about number lost to follow-up).
(3) information about exposure (1 point: results are given separate for different chemotherapy regimens, 0 points: results are not separated out for chemotherapy regimens).
(4) assessment of the outcome (2 points: measurement protocol for body weight, 1 point: body weight information for chart review or measurement without protocol, 0 points: no information on how body weight was assessed).
The rating system scores studies from 0 (low quality) to 6 points (high quality).

Overall estimate

Mean weight change reported in the papers ranged from -0.8 to 7.7 kg. A gain in body weight was reported in 31 of the 34 estimates, figure 3.2. The pooled mean weight change was 2.7 kg (95%CI: 2.0-3.3) with a heterogeneity of 94.2%. To further explore this high heterogeneity, stratified analyses were conducted.

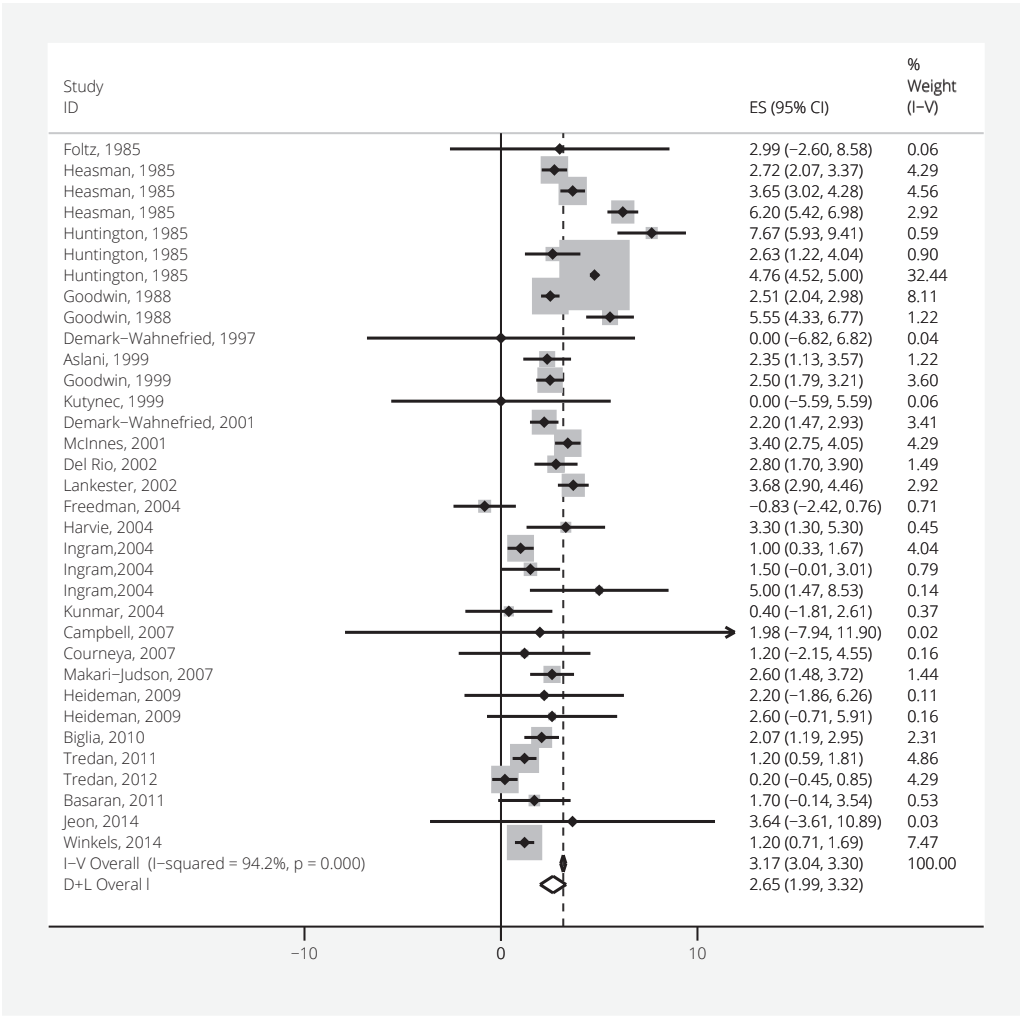

Figure 3.2. Weight change during chemotherapy for early stage breast cancer. Mean weight changes in individual estimates are depicted as squares with 95% confidence intervals (CI). Pooled estimates with 95%CI are depicted as open diamonds.

Stratified and sensitivity analyses

Body weight change estimates were stratified by type of chemotherapy, sample size, menopausal status, baseline BMI, study design, time between body weight measurements, year of publication, country, and study quality see table 3.3. Overall, weight gain was observed in all strata. Stratified analyses did not substantially reduce heterogeneity. The high heterogeneity remained for most subgroups except for the body weight change estimates in studies with a normal mean BMI at baseline (I^2=45.1%) who had a low heterogeneity and estimates not including CMF (I^2=74.7%), including studies with a mean BMI >25 at baseline (I^2=73.2%), and for prospective studies (I^2=69.5%), which all showed a moderate heterogeneity.

Sensitivity analyses excluding one study at a time did not markedly influence the overall result of weight change (range 2.4-2.8 kg) nor did importantly affect the amount of heterogeneity (range I^2 89.2-94.6%), neither did excluding the smallest or largest studies. In addition, excluding the intervention study did also not markedly influence the overall result of weight change 2.7 kg (95%CI: 2.0-3.4)[42].

Of the 21 body weight change estimates from studies published after 2000, 10 estimates included women treated with CMF. The main weight change in the body weight change estimates from studies after 2000 including women treated with CMF was 2.8kg (95%CI: 2.0, 3.5) compared to 1.0kg (95%CI: 0.5, 1.5) in those that did not include women treated with CMF.

Table 3.3. Stratified pooled mean weight change and 95% confidence interval in women during chemotherapy treatment for early stage breast cancer.

	No of estimates	Pooled weight change kg	95% CI [a]	I^{2} [b]
Overall				
All	34	2.7	2.0, 7.5	94.2
Type Chemotherapy				
CMF included	20	3.5	2.7, 4.3	93.7
No CMF	14	1.4	0.7, 2.0	74.7
Menopausal status				
Premenopausal	9	2.6	1.5, 3.6	86.9
Postmenopausal	2	1.3	-1.1, 3.7	89.4
Perimenopausal	1	4.8	4.5, 5.0	
Combination	22	2.7	2.0, 3.4	88.3
Baseline mean BMI				
20.0-24.9	6	0.5	-0.4 ; 1.3	45.1
25.0-29.9	15	2.4	1.8 ; 3.6	73.2
Unknown	13	3.5	2.6 ; 4.5	95.4
Follow-up				
end of chemotherapy / 6 months after baseline	26	2.7	2.0; 3.5	93.8
6 months after chemotherapy / 12 months after baseline	8	2.4	1.3; 3.4	90.9
Type of study				
Chart review	16	3.6	2.8, 4.4	94.8
Prospective	18	1.6	1.1, 2.2	69.5
Publication year				
Before and including 2000	13	3.8	2.9, 4.7	93.3
After 2000	21	1.9	1.3, 2.5	81.6
Sample Size				
≤100	23	3.0	2.2, 3.9	92.7
>100	11	2.1	1.3, 2.8	90.1
Country				
United States	10	2.8	1.6 ; 4.1	93.4
Canada	12	3.1	2.1 ; 4.1	91.8
Western Europe	9	2.0	1.1 ; 2.8	86.2
Australia	1	2.4	1.1 ;3.6	
Turkey	1	1.7	-0.1 ; 3.5	
Korea	1	3.6	-3.6 ; 10.9	
Study quality				
Low quality	11	2.9	1.6 ; 4.1	96.7
High quality	23	2.5	1.8 ; 3.2	88.8

[a] Confidence interval
[b] I^{2}= the percentage heterogeneity due to between-study variation

Meta-regression analysis

Results of the meta-regression analyses are shown in table 3.4. Results of the univariate model showed that weight gain was significantly different for body weight estimates from studies including CMF vs estimates from studies not including CMF, for studies using chart review vs prospective studies, and for studies published before 2000 vs studies published after 2000. In the multivariate model, we studied the combined effect of type of chemotherapy, study design and year of publication. In this model type of chemotherapy and year of publication remained significantly associated with body weight change, although the body weight change estimates were attenuated. Study design was no longer statistically significantly associated with body weight change in the multivariate model. The residual I^2 for the multivariable regression model was 84.8%, indicating that these factors explained only a small part of the heterogeneity.

Table 3.4. Results from multivariate meta-regression analysis on weight change in subgroups of early stage breast cancer patients during chemotherapy

	Unadjusted				Adjusted[d]			
	RC[a]	SE[b]	95% CI[c]	P-value	RC[a]	SE[b]	95% CI[c]	P-value
Type chemotherapy								
No CMF	ref				ref			
CMF included	2.2	0.6	1.1, 3.3	<0.01	1.4	0.6	0.3, 2.6	0.02
Menopausal status								
Premenopausal	ref							
Postmenopausal	-1.3	1.4	-4.1, 1.5	0.36				
Perimenopausal	2.2	1.8	-1.5, 5.8	0.23				
Combination	0.1	0.8	-1.5, 1.6	0.91				
Follow-up								
end of chemotherapy / 6 months after baseline	ref							
6 months after chemotherapy / 12 months after baseline	-0.1	0.1	-0.3 ; 0.2	0.64				
Type of study								
Chart review	ref				ref			
Prospective	-2.0	0.6	-3.1, -0.8	<0.01	-0.7	0.6	-1.9, 0.5	0.24
Publication year								
After 2000	ref				ref			
Before and including 2000	1.9	0.6	0.8, 3.1	<0.01	1.3	0.5	0.2, 2.3	0.02
Sample Size								
≤100	ref							
>100	-1.0	0.7	-2.3, 0.4	0.15				
Country								
United States	ref							
Canada	-0.2	0.9	-1.5 ; 2.0	0.79				
Western Europe	-0.8	0.9	-2.6 ; 1.0	0.39				
Australia	-0.5	1.9	-4.5 ; 3.5	0.80				
Turkey	-1.1	2.1	-5.4 ; 3.1	0.58				
Korea	0.8	4.1	-7.7 ; 9.3	0.85				
Quality assessment								
Low Quality	ref							
High Quality	-0.4	0.7	-1.8 ; 1.0	0.58				

[a] Regression coefficient
[s] Standard error
[c] Confidence interval
[d] Adjusted for, type of chemotherapy, type of study and publication year

Discussion

The present work is the first meta-analysis that quantified changes in body weight during chemotherapy in women with early stage breast cancer. Based on 25 papers, a mean weight gain of 2.7 kg (95%CI: 2.0-3.3) was observed with a heterogeneity of 94.2%. Stratified analysis showed weight gain in all strata, but the strata could only marginally explain the heterogeneity. Adjusted weight gain estimates based on body weight estimates from studies including patients treated with CMF and papers published before 2000 were larger compared to estimates from studies in which CMF was not included and papers published after 2000. Despite the high heterogeneity which could only partly be explained, the results of this meta-analysis suggest constant and significant weight gain during chemotherapy for women with early stage breast cancer.

Treatment for breast cancer has changed over time. Before the 1990s, only CMF was used as chemotherapy regime, while during the 90s the use of anthracyclines gradually increased. In studies after 2004, taxane-based chemotherapy was introduced as a treatment for early stage breast cancer. In the current meta-analysis, CMF emerged as a chemotherapy associated with weight gain, which use has importantly decreased over time. However, our meta-analyses also showed that in studies published after the year 2000 the mean weight gain was still considerable 1.3 kg. Stratified by type of chemotherapy, the mean weight change from studies published after 2000 and including women treated with CMF was 2.8 kg compared to 1.0 kg in those that did not include women treated with CMF. These data suggest that the abandoning of CMF as the chemotherapeutic regimen of choice could be an important reason for observing less weight gain in more recent studies. Independently of CMF, time of publication was associated with weight gain. A possible reason why studies after 2000 observed less weight gain relative to earlier studies could be the incremental use of taxanes in more recent years. However, as the studies included in this meta-analysis did not all provide detailed information on type of chemotherapy, we can only speculate on that.

Another possible explanation for differences in weight gain between older and more recent studies could be age and BMI at baseline. However, we did not see a difference in baseline age and mean BMI comparing older and more recent studies. Yet, since most studies included in

this meta-analysis did not provide detailed information and stratified results on baseline BMI, we could not explore this in detail.

Weight gain appeared to be less in prospective studies than in chart review studies in our meta-analysis. A possible explanation for this finding is, that in prospective studies, data usually were collected as part of a cohort or other observational study. These studies could potentially include a selected (e.g. high SES) population, which make them less generalizable to the general population. Chart review papers usually included all patients treated with chemotherapy in a retrospective period of time, but completeness of data was not clearly reported in all studies. Thus both, chart reviews and prospective studies may suffer from incomplete data and selection issues, but as studies did not provide detailed information on response rates and possible selection, we could not explore this further in our meta-analysis. Moreover, stratified results on study quality did not show any differences between studies considered as low quality compared to studies considered of high quality, neither did stratifying on study quality reduce heterogeneity.

An earlier narrative review suggested that women with a normal BMI at baseline were more likely to gain weight compared to women who were overweight at diagnosis[15], however other studies did not confirm this[37,44]. Since only one study included in this meta-analysis reported results for weight change stratified in categories of baseline BMI, we could not study this in great detail. Nevertheless, our analyses suggested a lower weight gain in studies with a mean normal BMI at baseline compared to studies with mean BMI > 25 at baseline. These results should be interpreted carefully, since they represents mean BMI for the total study, which does not mean that all women in that study fall within that BMI category. If the mean BMI of a study population is lower, other possible confounding factors may also differ from studies in which mean BMI is higher. However, as this is speculative, and data on other confounding factors is limited, we could not study this further. An important factor in the interpretation of our results is that heterogeneity of our estimates remained high despite elaborate analyses to explore possible sources of heterogeneity, including stratification and meta-regression. This high heterogeneity suggests that other, less studied factors may importantly contribute to weight

gain during chemotherapy. A factor that could contribute is ovarian failure which is especially relevant for premenopausal women. This ovarian failure impacts hormonal levels, which may possibly be related to subsequent weight gain. Nevertheless, in the current meta-analyses we did not observe differences in weight gain between pre- and postmenopausal women, possibly because only a small part of the studies stratified for menopausal status[48]. Weight gain may also be explained by common side-effects of chemotherapy such as fatigue, potentially reducing habitual physical activity[17,49]. Recently, special programs are implemented in breast cancer care in various countries stimulating physical activity. These added interventions may explain differences between older and more recent studies. Also, chemotherapy may induce changes in taste and smell possibly leading to changes in dietary eating patterns which could influence body weight[50]. However, little research has focused on these sensory effects. Furthermore, reductions in energy expenditure in rest have been reported during and after chemotherapy which may lead to an increase in body weight[15,51]. As most studies did not publish on these potential factors, we could not explore whether they were possible sources of heterogeneity in our meta-analysis.

A limitation of our study is that we could not explore duration of chemotherapy as a source of heterogeneity. Chemotherapy duration has decreased nowadays. Literature suggest that duration of chemotherapy could be an important factor to weight gain[15,17,51]. In this meta-analyse it was not possible to explore this since most studies did not report the duration of chemotherapy.

Another limitation is that we used the year that the manuscript was published and not the years the participants were enrolled into the study: time between conducting the study and publishing the results may vary between studies. Although year of enrolment would have been preferable, for 13 estimates this information was available. A sensitivity analysis using only the 21 estimates that had this information available showed a comparable trend of a decrease in weight gain for more recent studies (data not shown).

Also we could only study changes in weight, but not in fat or fat-free mass. Future studies should provide more detailed information on body weight trajectories and preferably body composition,

as changes in fat and lean mass may be more clinically relevant. In addition, future studies should also report percentage of women with a significant weight loss, gain or maintenance rather than only mean weight change, so it is possible to establish the clinical magnitude of changes in body weight during chemotherapy.

A strength of this study is that it is, to the best of our knowledge, the first meta-analysis conducted on weight gain in breast cancer women during chemotherapy. A comprehensive literature search was conducted including an additional hand search. This makes the potential of missing any published data in English unlikely.

In conclusion, our results indicate that women generally gain weight during chemotherapy for early stage breast cancer. This weight gain is more pronounced in women treated with CMF and is greater in studies published before 2000. Although weight gain after chemotherapy has decreased over the course of time, weight gain is still substantial and deserves clinical attention.

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Additional file 3.1. Search Strategy

PUBMED

Weight changes

Body weight change [mesh] OR body weight changes [mesh] OR body weight [tiab] OR weight* [tiab]

Breast cancer

breast cancer [mesh] OR breast cancer [tiab] OR malign* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR cancer* [tiab] OR tumor* [tiab] OR tumour* [tiab] AND breast* [tiab] or mamma* [tiab]

Chemotherapy

chemotherapy [mesh] OR chemo* [tiab] OR cytostatic [mesh] OR cytostatic* [tiab]

SCOPUS

Weight change

(TITLE-ABS-KEY (body weight change*) OR TITLE-ABS-KEY (body weight*) OR TITLE-ABS-KEY (weight change*))

Breast caner

((TITLE-ABS-KEY (malign*) OR TITLE-ABS-KEY (neoplasm*) OR TITLE-ABS-KEY (carcinoma*) OR TITLE-ABS-KEY (cancer*) OR TITLE-ABS-KEY (tumor*) OR TITLE-ABS-KEY (tumour*))) AND ((TITLE-ABS-KEY (breast*) OR TITLE-ABS-KEY (mamma*)))

Chemotherapy

(TITLE-ABS-KEY (chemo*) OR TITLE-ABS-KEY (cytostatic*))

EMBASE

Weight change

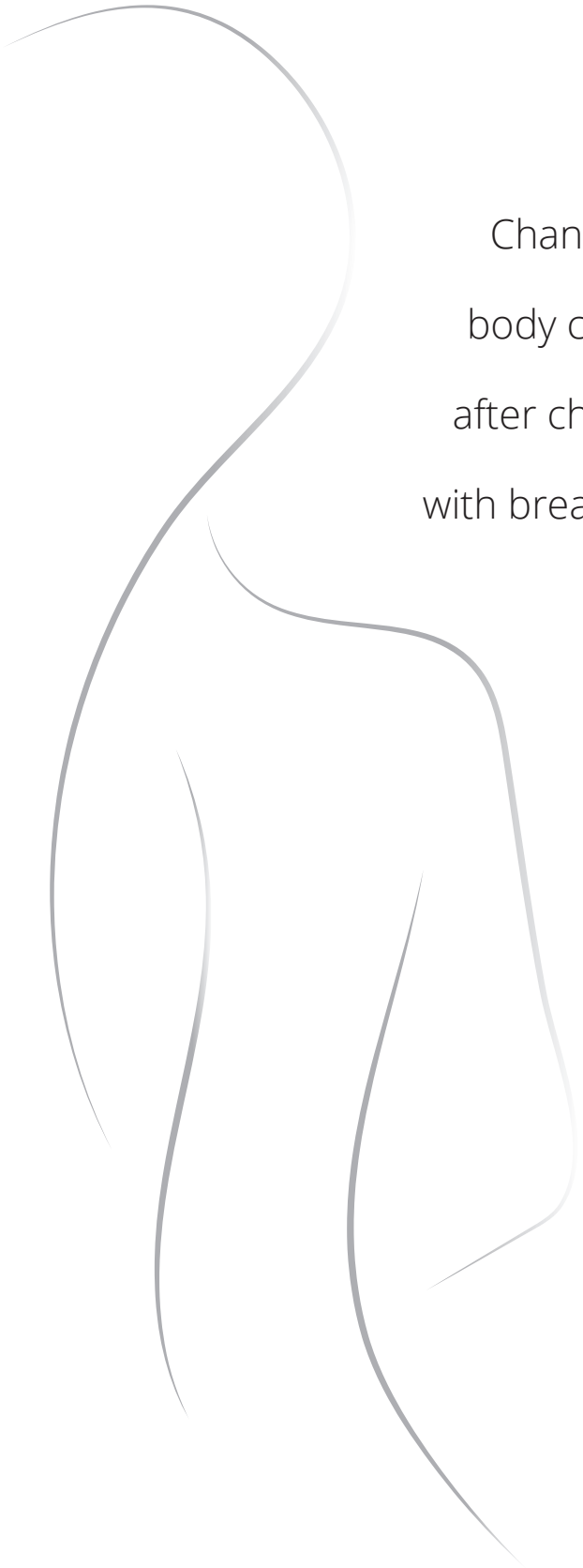
Exp 'body weight change'/ OR body weight changes. ti,ab OR body weight change*. ti,ab OR body weight. ti,ab

Breast cancer

exp 'breast cancer'/ OR breast cancer. ti,ab OR malign*. ti,ab OR neoplasm*. ti,ab OR carcinoma*. ti,ab OR cancer*. ti,ab OR tumor*. ti,ab OR tumour*. ti,ab AND breast*. ti,ab OR mamma*.

Chemotherapy

exp 'chemotherapy/ OR chemo*. ti,ab OR exp cytostatics/ OR cytostatic*. ti,ab



Chapter 4

Changes in body weight and body composition during and after chemotherapy in women with breast cancer compared to women without cancer

M.M.G.A. van den Berg,
M. Visser,
J.H.M. de Vries,
E. Kampman,
R.M. Winkels.

Abstract

Background: Several studies suggested that body weight and body composition change during chemotherapy for breast cancer, with an increase in fat mass and a loss or no change in lean body mass. However, many of these studies did not include a comparison group and could not assess whether these changes differ from natural age-related changes in body weight and body composition.

Aim: To describe the extent and patterns of changes in body weight and body composition in breast cancer patients during chemotherapy and 6 months after chemotherapy compared to age-matched women without cancer. In addition, we identified which determinants were associated with the changes in body weight and body composition.

Methods: We recruited 145 newly diagnosed breast cancer patients (stage I-IIIB) and 121 women without cancer of a similar age (range +/- 2 years). Body composition was assessed using a Dual Energy X-ray Absorptiometry (DEXA)-scan before start of chemotherapy, shortly after chemotherapy, and 6 months after chemotherapy within the patient group and at three time points six months apart within the comparison group.

Results: Shortly after chemotherapy, patients had a significantly higher body weight, BMI and lean body mass than women in the comparison group, while fat mass was similar. Six months after chemotherapy no differences in body weight, BMI, fat mass and lean body mass were observed between the patient and comparison group. In multivariate analyses, a younger age, better appetite during chemotherapy, and negative ER-receptor status of the tumor were associated with greater changes in body weight over time in the patients. A younger age and better appetite during chemotherapy were also associated with greater changes in fat mass over time, while only a better appetite was associated with greater changes in lean body mass over time.

Conclusions: This study showed that in the period from start of chemotherapy until 6 months after the end of chemotherapy changes in body weight and body composition were minimal in women with breast cancer, and did not differ from natural changes over time in women of a similar age without breast cancer.

Introduction

Several reviews described that women with breast cancer gain weight during chemotherapy[1-7]. Our recent meta-analysis showed that women with breast cancer gain 2.7 kg body weight during chemotherapy[8]. Additionally, the meta-analysis suggested that weight gain was most pronounced in patients receiving cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimes –regimes that are currently being used less often- and that weight gain was less pronounced in patients treated with more recent types of chemotherapy[8].

To date it is unknown which factors contribute to weight gain during chemotherapy. Suggested factors described are treatment-induced ovarian failure accompanied by the rapid onset of menopause[9] as well as reductions in physical activity[3,5,10-12]. Other factors suggested to be associated with weight change during chemotherapy include, premenopausal status at diagnosis[1,3,13,14], younger age at diagnosis[1,10,15] a normal BMI before start of chemotherapy[1,16], and a high BMI and higher fat mass before start of chemotherapy[17]. Also changes in resting energy expenditure[6,12,18,19] and dietary intake[5,6,18,19] are described as possible factors associated with changes in body weight and body composition.

Besides body weight gain, changes in body composition during chemotherapy have been reported, consisting of an increase in fat mass with a loss or no change in lean body mass, even in weight stable patients[1-4,20]. Changes in body weight and body composition are important, since it is suggested that these changes are associated with recurrence and mortality, however, not all studies show consistent results[21-23].

Earlier studies that investigated changes in body composition during chemotherapy in breast cancer patients mostly included a small study sample of 8 to 76 patients[5,12,13,16,17,24-31]. More importantly, most of these studies did not compare the changes in body weight and body composition in breast cancer patients to a comparison group of women without cancer[5,12,13,16,17,24-27,29-31]. The only study that included a comparison group concluded that women with breast cancer did not significant change in body weight during the first year of their treatment in comparison to the comparison group. However, patients underwent unfavourable

changes in body composition, with an increase in fat mass and decrease in fat-free mass and lean soft tissue[28].Therefore, based on current literature, it is still unclear whether changes in body weight and composition in breast cancer patients are indeed treatment related or due to natural fluctuations over time.

The objective of this study was to describe the extent and patterns of changes in body weight and body composition in breast cancer patients (stage I-IIIB) from start of chemotherapy until 6 months after chemotherapy compared to an age-matched comparison group without cancer. In addition, we investigated potential determinants of these changes in body weight and body composition in breast cancer patients.

Materials and Methods

Study population

The analyses were done using data of the COBRA-study, an observational multi-centre study which compares women with breast cancer treated with chemotherapy with women without cancer who are of similar age (range +/- 2 years) [32]. Women with newly diagnosed, stage I-IIIB, operable breast cancer, who were scheduled for 2nd or 3rd generation neo- adjuvant chemotherapy were included. Eligible patients were recruited via the staff of 11 participating hospitals in the Netherlands prior to commencement of chemotherapy. Participants in the comparison group were recruited via patients; patients were asked to distribute envelopes with study information to friends, acquaintances and colleagues. Women without cancer interested in participating in the study contacted the researchers and were consented for participating by the researchers. All study participants needed to be at least 18 years old and able to communicate in Dutch. Exclusion criteria for both groups were: history of cancer, previous treatment with chemotherapy, (intended) pregnancy, dementia or other mental conditions that made it impossible to comply with the study procedures.

For the current study, we included 145 breast cancer patients and 121 women without cancer of the COBRA-study recruited between May 01, 2013 and December 31, 2015.

The protocol was approved by the Medical Ethical Committee of Wageningen University. All participants provided written informed consent before enrolment.

Study design

Measurements took place at three time points during the study period for all participants. For the patient group, these time points were: before start of chemotherapy or during the first cycle of chemotherapy (T1), shortly after chemotherapy (T2), and 6 months after chemotherapy (T3). For the comparison group these measurements were conducted over a similar timeframe: baseline (T1), 6 months after baseline (T2), and 12 months after baseline (T3).

Measurements

Body weight and body composition

Body weight and body composition were assessed using a Dual-Energy X-ray Absorptiometry (DEXA)-scan at all three time points. Participants were measured 3 times in the same hospital using the same scanner by trained technicians using a total body scan protocol. From the total body DEXA-scan, body weight (kg), total body fat mass (kg), and total lean body mass (kg) were obtained. In addition, lean body mass (kg) of the arms, legs, and torso were obtained. In 60 participants body weight was also measured using a calibrated scale on all three time points.

Physical activity

Information regarding physical activity was derived from the validated Short Questionnaire to ASess Health enhancing physical activity (SQUASH) at all three time points[33,34]. In this questionnaire, participants were asked to report their average time (days per week, hours and minutes per day) spent in walking, cycling, gardening, odd-jobs, sport, household activities and work. Based on the self-reported intensity level of each activity a metabolic equivalent (MET) value was assigned[35]. According to the Dutch physical activity guideline, 4.0 MET was used as a lower cut off for moderate activity for those aged <55 y. For older women a lower cut off of 3.5 MET was used[36]. These values were presented as MET-hours per week.

Dietary intake

A food frequency questionnaire (FFQ) was used to assess habitual intake at baseline (T1)[37,38]. In addition, in patients we assessed scores on eating styles (restrained, emotional, external) using the Dutch Eating Behaviour Questionnaire (DEBQ)[39]. Based on these scores, patients were categorized in high versus low groups for each eating style.

Appetite, taste, smell, and symptoms during chemotherapy

In patients only appetite, taste, and smell during chemotherapy were assessed using the Appetite, Hunger feelings and Sensory Perception (AHSP) questionnaire[40]. A higher score on appetite, taste or smell corresponds with a more positive judgement about current appetite, taste, or smell.

The presence of the following symptoms were assessed two times during chemotherapy: pain; dry mouth; feeling depressed; thick saliva; diarrhoea; sore mouth; lack of energy; nausea; difficulty chewing; difficulty swallowing; anxiety; constipation and vomiting. For each symptom the question was asked: 'How often have you experienced this symptom during the past three days?', scored on a 5 point Likert scale, ranging from 1="not at all" to 5="a lot". If a symptom scored 1 this symptom was absent while a score of 2 to 5 was coded as presence of the symptom. The mean score of total number of symptoms present of the two moments was calculated. A higher total score corresponds with more reported symptoms.

Demographic, personal and medical information

At T1 all participants filled out a questionnaire for demographic information, including body height, age, menopausal status, smoking status and educational level. BMI was calculated based on self-reported body height and body weight from DEXA-scan. Information on stage of cancer at diagnosis, tumour characteristics, and treatment were obtained from reviewing patients' medical records using a standardized form.

Data analyses

Population characteristics were described as median with an interquartile range (IQR) or number with percentage for the patient and comparison group separately. To assess differences in the characteristics between groups, the Mann-Witney U-test was used for continuous data and the Chi Square test for categorical data.

Differences in body weight and body composition between the patient and comparison group over time were analysed using Linear Mixed Models, with time, group and their interaction term as fixed factors and subjects as random factors in the model.

In patients only, potential determinants of changes in body weight, body fat mass and lean body mass over time were assessed using Linear Mixed Models.

Potential determinants were included in the model as an interaction term with time. We assessed; 1) baseline demographic and lifestyle determinants (age, education level, smoking status, physical activity, intake of energy, protein, carbohydrate, fat and alcohol, and eating style); 2) clinical determinants (stage, adjuvant vs neo-adjuvant treatment, type of chemotherapy, receptor status, hormone treatment); 3) determinants during chemotherapy (baseline measurements before/during chemotherapy, appetite, taste, smell, and number of symptoms). Significant determinants were subsequently included in a multivariate model.

Linear Mixed Models estimated means and standard errors, presented as mean ± SE. In all models, a random intercept and slope model was used with appropriate covariates and covariance structure. Using a top-down model fitting procedure, the appropriate covariates and covariance structure were chosen. These differed between the various outcome variables.

In 60 participants we measured body weight using a scale and DEXA-scan, at all three time points. As an additional analysis, we compared whether changes in body weight over time differed between these two methods, using an independent T-test.

In all analyses, a p-value <0.05 was considered significant. Statistical analyses were performed in SAS 9.4 (SAS Institute, Cary NC).

Results

Population characteristics

At baseline (T1), the patient and comparison group were similar in age, smoking status, physical activity, dietary intake, and menopausal status, while there were significantly more high educated women in the comparison group than in the patient group, see table 4.1. Women in the patient group had a significantly higher BMI, total lean body mass (kg), fat mass in the arms (kg), and fat mass in the legs (kg) compared to women in the comparison group. Shortly after chemotherapy and 6 months after chemotherapy women with breast cancer reported a significantly lower physical activity than women without cancer in the same time period.

Table 4.1. Demographic and body composition characteristics of breast cancer patients and the comparison group of women without cancer included in the study presented as median (IQR) or n (%).

Characteristics	Patient group (n=145)	Comparison group (n=121)
Demographics		
Age, yrs (median, IQR)	51.9 (47.7 ; 59.0)	52.2 (46.7 ; 62.0)
Menopausal status (n, %)		
Premenopausal	57 (39.3)	52 (43.0)
Menopausal	20 (13.8)	10 (8.3)
Postmenopausal	66 (45.5)	59 (48.8)
Missing	2(1.4)	0
*Education level (n, %)**		
Low	14 (9.7)	9 (7.4)
Medium	49 (33.8)	28 (23.1)
High	80 (52.4)	83 (68.6)
Missing	6 (4.1)	1 (0.8)
Smoking status (n, %)		
Current	25 (17.2)	10 (8.3)
Former	60 (41.4)	57 (47.1)
Never	54 (37.2)	53 (43.8)
Missing	6 (4.1)	1 (0.8)
Physical activity		
MET-H/week at baseline (median, IQR)	139.1 (82.7 ; 172.5)	136.7 (104.5 ; 183.4)
MET-H/week shortly after chemotherapy / 6 months after baseline (median, IQR)*	54.2 (25.5 ; 87.7)	127.8 (72.2 ; 165.3)
MET-H/week end of study (median, IQR)*	81.4 (44.2 ; 133.6)	125.6 (68.5 ; 178.9)
Dietary intake		
Energy, kcal (median, IQR)	1979 (1674 ; 2333)	1966 (1670 ; 2336)
Protein, percentage (median, IQR)	15.7 (14.0 ; 17.3)	15.2 (14.1 ; 16.8)
Fat, percentage (median, IQR)	36.9 (33.6 ; 41.0)	36.4 (33.3 ; 40.6)
Carbohydrates, percentage (median, IQR)	42.1 (38.3 ; 45.5)	41.5 (38.2 ; 44.9)
Alcohol, percentage (median, IQR)	1.1 (0.0 ; 3.6))	2.3 (0.6 ; 5.0)
Baseline body composition		
Height cm (median, IQR)	167.0 (163.5 ; 172.5)	169.0 (165.0 ; 172.5)
Weight kg (median, IQR)	69.9 (62.9 ; 81.0)	69.8 (62.7 ; 77.2)
BMI kg/m^2 (median, IQR)*	25.4 (22.3 ; 29.0)	24.0 (22.2 ; 26.8)
Total fat mass kg (median, IQR)	25.6 (20.0 ; 32.5)	24.2 (19.4 ; 29.8)
Total fat mass % (median, IQR)	36.4 (31.2 ; 41.8)	34.5 (30.7 ; 39.9)
Arms fat kg (median, IQR)*	2.9 (2.3 ; 3.8)	2.7 (2.0 ; 3.4)
Legs fat kg (median, IQR)	9.4 (8.0 ; 12.1)	8.7 (7.0 ; 10.8)
Trunk fat kg (median IQR)	11.4 (8.5 ; 16.1)	11.4 (8.7 ; 14.5)
Total lean mass kg (median, IQR)*	42.6 (39.2 ; 46.6)	43.9 (40.0 ; 46.2)
Arms lean kg (median, IQR)	4.2 (3.8 ; 4.7)	4.3 (3.9 ; 4.8)
Legs lean kg (median IQR)*	13.8 (12.8 ; 15.4)	14.3 (12.9 ; 15.5)
Trunk lean kg (median, IQR)	22.0 (19.4 ; 23.8)	21.7 (20.1 ; 23.1)

* Indicates a significant difference between the groups at p<0.05.

Changes in body weight and body composition

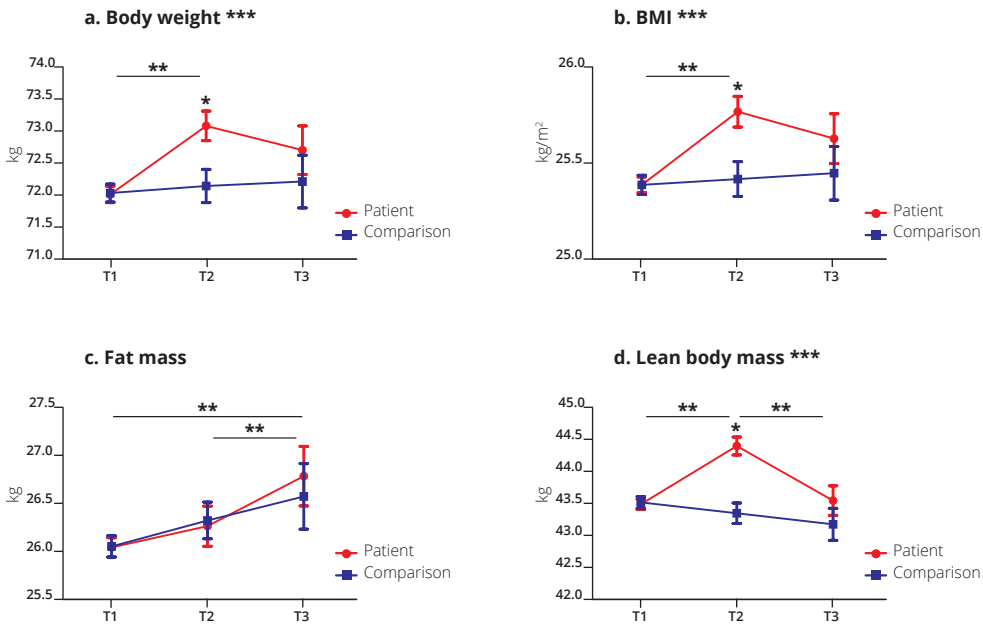
Adjusted changes in body weight and body composition over time are presented in Figure 4.1. At baseline (T1) there was no difference in body weight and body composition between the patient and comparison group. In the comparison group, no significant changes in body weight or body composition over time were observed.

Body weight differentially changed over time between women with breast cancer and women without cancer (figure 4.1a). Breast cancer patients significantly increased in body weight from baseline (T1) to shortly after chemotherapy (T2) (T1: 72.0 kg ± 0.13 kg, T2: 73.1 kg ± 0.23 kg). However, 6 months after chemotherapy (T3) body weight had decreased (72.7 kg ± 0.38 kg). Compared to women without cancer, women with breast cancer had a significant higher body weight shortly after chemotherapy (T2), but not at 6 months after chemotherapy (T3). Similar results were obtained for BMI (figure 4.1b).

Fat mass did not differentially change over time between patients and women without cancer (figure 4.1c). From baseline (T1) to shortly after chemotherapy (T2) breast cancer patients had a stable fat mass. At T3, 6 months after chemotherapy, among patients fat mass slightly yet significantly increased compared to baseline (T1) and shortly after chemotherapy (T2) (T1: 26.1 kg ± 0.10 kg, T2: 26.3 kg ± 0.27 kg, T3: 26.8 kg ± 0.31 kg).

At baseline (T1) there was no difference in lean body mass between women with breast cancer and women without cancer. Lean body mass differentially changed over time in patient versus comparison group (figure 4.1d). In the patient group, lean body mass significantly increased from baseline (T1) to shortly after chemotherapy (T2), but returned to baseline values at 6 months after chemotherapy (T3) (T1: 43.5 kg ± 0.08 kg, T2: 44.4 kg ± 0.14 kg, T3: 43.5 kg ± 0. 23 kg). At T2 women in the patient group had a significant higher lean body mass compared to women without cancer but at T3 lean body mass in the patient group was not different from lean body mass in the comparison group.

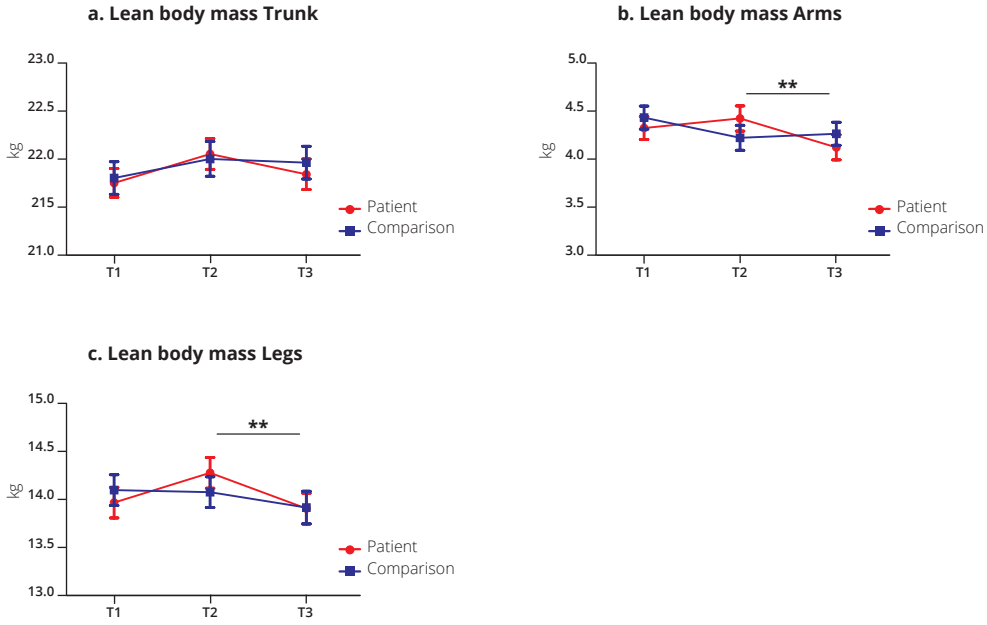
Changes in lean body mass of the trunk, arms and legs of the patient group showed similar trends as were observed in total body lean mass: an increase from baseline (T1) to shortly after chemotherapy (T2), and back to baseline values 6 months after chemotherapy (T3) (figure 4.2). There was no difference in the changes over time between the patient and comparison group. Table 4.2 shows the results of measurements body weight using a scale and DEXA-scan. Results showed that DEXA-scan slightly underestimated body weight compared to scale. However more importantly, changes in body weight did not differ between scale and DEXA-scan measurements.



Body weight (a) and BMI (b) are adjusted for: age, education level, baseline value ,age*group,
Fat mass (c) and lean body mass (d) are adjusted for: age, education level, BMI, baseline value, age*group,

* indicates a significant differences at this time point between the two groups at p <0.05.
** indicates a significant difference over time in the patient group at p <0.05.
*** indicates a significant difference over time between the patient group and comparison group at p<0.05

Figure 4.1. Body composition (mean ± SE) over time for the breast cancer patients and comparison group without cancer. T1 represents before chemo (patients) and baseline (comparison), T2 represents shortly after chemotherapy (patients) and after 6 months (comparison). T3 represents a half year after chemotherapy (patients) and after 12 months (comparison).



Adjusted for age, education level, baseline value, age*group
* indicates a significant differences between the two groups at p <0.05.
** indicates a significant difference over time in the patient group at p <0.05.
*** indicates a significant difference over time between the patient group and comparison group at p<0.05

Figure 4.2. Lean body mass for the Trunk, Arms and Legs (mean ± SE) over time for the patient and comparison group. T1 represents before chemo (patients) and baseline (comparison), T2 represents shortly after chemotherapy (patients) and after 6 months (comparison). T3 represents a half year after chemotherapy (patients) and after 12 months (comparison).

4

Table 4.2. Results of body weight measurements by scale and DEXA-scan over time presented as mean (SD). Table A presents the mean body weight at different time points, while table B presents the changes between the different time points. T1 represents before chemotherapy (patients) and baseline (comparison), T2 represents shortly after chemotherapy (patients) and after 6 months (comparison), T3 represents 6 months after chemotherapy (patients) and after 12 months (comparison).

A. Body weight	**T1 *(n=60)***	**T2 *(n=60)***	**T3 *(n=60)***
Scale measurement	71.7 (11.2)	72.1 (11.6)	71.9 (12.4)
DEXA measurement	71.2 (11.3)	71.6 (11.5)	71.3 (12.1)

B. Changes in body weight	**Scale measurement**	**DEXA measurement**	**P-value**
T1 – T2	0.5 (2.7)	0.3 (2.6)	0.82
T1 – T3	0.3 (4.1)	0.1 (3.6)	0.82
T2 – T3	-0.2 (3.1)	-0.3 (2.8)	0.93

Determinants of changes in body weight, body fat mass, and lean body mass

Table 4.3 shows results of the associations between possible determinants and changes in body weight, fat mass, and lean body mass in breast cancer patients. In the multivariate analyses, a younger age, better appetite during chemotherapy and ER-receptor negative tumour were associated with changes in body weight. Determinants associated with changes in fat mass were a younger age and better appetite during chemotherapy, while only a better appetite during chemotherapy was associated with changes in lean body mass.

Table 4.3. Determinants associated with changes in body weight, fat mass and lean body mass in the patient group over time

	Changes in body weight		Changes in fat mass		Changes in lean body mass	
	Adjusted[+]	Multivariate[$]	Adjusted[++]	Multivariate[$$]	Adjusted[+++]	Multivariate[$$$]
	β_1 (95% CI)	β_1 (95% CI)	β_1 (95% CI)	β_1 (95% CI)	β_1 (95% CI)	β_1 (95% CI)
Age, *yrs*	-0.0 (-0.1 ; -0.0)*	-0.0 (-0.1 ; -0.0)*	-0.0 (-0.0 ; -0.0)*	-0.0 (-0.0 ; -0.0)*	-0.0 (-0.0 ; 0.0)	
Education level						
Low	0.0 (-0.5; 0.5)		-0.2 (-0.6 ; 0.2)		0.3 (-0.1 ; 0.6)	
Middle	0.0 (-0.3 ; 0.4)		-0.1 (-0.3 ; 0.2)		0.1 (-0.1 ; 0.3)	
High	REF		REF		REF	
Smoking status						
Current	-0.1 (-0.5 ; 0.4)		-0.1 (-0.5 ; 0.2)		0.0 (-0.2 ; 0.3)	
Former	-0.1 (-0.4 ; 0.2)		0.1 (-0.2 ; 0.3)		-0.1 (-0.3 ; 0.1)	
Never	REF		REF		REF	
Physical activity, *5 METh-week*	0.0 (-0.0 ; 0.0)		-0.0 (-0.0 ; 0.0)		-0.0 (-0.0 ; 0.0)	
Dietary intake, *100 kcal*						
Energy	0.0 (-0.0 ; 0.0)		0.0 (-0.0 ; 0.0)		-0.0 (-0.0 ; 0.0)	
Protein	0.1 (-0.1 ; 0.3)		0.1 (-0.1 ; 0.2)		-0.0 (-0.1 ; 0.1)	
Carbohydrate	0.0 (-0.0 ; 0.1)		0.0 (-0.0 ; 0.1)		0.0 (-0.0 ; 0.1)	
Fat	0.0 (-0.0 ; 0.1)		0.0 (-0.0 ; 0.1)		-0.0 (-0.0 ; 0.0)	
Alcohol	-0.1 (-0.3 ; 0.1)		-0.0 (-0.2 ; 0.1)		-0.0 (-0.2 ; 0.1)	
Restraint eating style						
Low	-0.1 (-0.7 ; 0.4)		-0.1 (-0.4 ; 0.2)		-0.1 (-0.3 ; 0.1)	
High	REF		REF		REF	
Emotional eating style						
Low	-0.4 (-1.2 ; 0.3)		-0.3 (-0.6; 0.1)		-0.2 (-0.5 ; 0.1)	
High	REF		REF		REF	
Extern eating style						
Low	-0.1 (-0.6 ; 0.4)		-0.0 (-0.3 ; 0.2)		0.0 (-0.2 ; 0.2)	
High	REF		REF		Ref	
Cancer determinants						
Staging						
I	0.3 (-0.3 ; 0.8)		0.3 (-0.1 ; 0.7)		-0.0 (-0.2 ; 0.4)	
II	0.1 (-0.4 ; 0.6)		-0.0 (-0.3 ; 0.3)		0.1 (-0.2 ; 0.4)	
III	REF		REF		REF	
Timing baseline						
Before chemotherapy	-0.0 (-0.5 ; 0.4)		-0.1 (-0.4 ; 0.2)		0.0 (-0.2 ; 0.3)	
First cycle	REF		REF		REF	

Chemotherapy						
Adjuvant	-0.2 (-0.5 ; 0.1)		-0.0 (-0.2 ; 0.2)		-0.1 (-0.3 ; 0.1)	
Neo-adjuvant	REF		REF		REF	
Type of chemotherapy						
Sequential	-0.1 (-0.4 ; 0.2)		-0.0 (-0.2 ; 0.2)		-0.0 (-0.2 ; 0.1)	
Combined	REF		REF		REF	
ER-status						
Negative	0.4 (0.0 ; 0.8)*	0.4 (0.0 ; 0.9)*	0.2 (-0.1 ; 0.4)		0.2 (0.0; 0.4)*	0.1 (-0.2 ; 0.3)
Positive	REF		REF		REF	
PR-status						
Negative	0.2 (-0.2 ; 0.5)		0.0 (-0.2 ; 0.3)		0.2 (-0.0 ; 0.3)	
Positive	REF		REF		REF	
HER2-status						
Negative	0.0 (-0.4 ; 0.4)		-0.1 (-0.4 ; 0.2)		0.1 (-0.2; 0.3)	
Positive	REF		REF		REF	
Triple negative tumour						
No	-0.1 (-0.5; 0.4)		0.1 (-0.2 ; 0.4)		-0.2 (-0.4 ; 0.1)	
Yes	REF		REF		REF	
Hormone treatment						
No	0.2 (-1.0 ; 1.3)		-0.1 (-1.0 ; 0.7)		0.3 (-0.3 ; 1.0)	
Yes	0.4 (-0.8 ; 1.6)		-0.0 (-0.9 ; 0.8)		0.5 (-0.2 ; 1.2)	
Unknown	REF		REF		REF	
Determinants during chemotherapy						
Appetite score	0.1 (0.0 ; 0.1)*	0.1 (0.0 ; 0.1)*	0.0 (0.0 ; 0.1)*	0.0 (0.0 ; 0.1)*	0.0 (0.0 ; 0.0)*	0.0 (0.0 ; 0.0)*
Taste score	0.0 (-0.0 ; 0.0)		0.0 (-0.0 ; 0.0)		0.0 (-0.0 ; 0.0)	
Smell score	0.0 (-0.0 ; 0.1)		0.0 (-0.0 ; 0.0)		0.0 (-0.0 ; 0.0)	
Number of symptoms	0.0 (-0.0 ; 0.1)		0.0 (-0.0 ; 0.1)		-0.0 (-0.1 ; 0.0)	

+ Adjusted for baseline body weight determinant*time
++ Adjusted for baseline BMI, baseline fat mass, determinant*time
+++ Adjusted for baseline BMI, baseline lean body mass, determinant*time
$ Adjusted for baseline body weight, age*time, ER-status*time, appetite*time
$$ Adjusted for baseline BMI baseline fat mass, age*time, appetite*time
$$ Adjusted for baseline BMI baseline lean body mass, ER-status*time, appetite*time
* p<0.05

Discussion

In our study we found that, from baseline to shortly after chemotherapy, patients experienced an increase in body weight, BMI and lean body mass, but not fat mass, compared to women without cancer. However, 6 months after chemotherapy we did no longer find a difference in body weight, BMI, lean body mass, and fat mass in the patient group compared to the women without cancer. These results suggest that the observed increases in body weight and change in body composition during chemotherapy in the patient group are temporary.

A second objective of our study was to identify potential determinants of the changes in body weight and body composition in breast cancer patients over time. Our multivariate results suggest that a younger age, better appetite during chemotherapy, and an ER-receptor negative tumour were associated with greater changes in body weight over time. A younger age and better appetite during chemotherapy were associated with greater changes in fat mass over time, while the only determinant associated with greater changes in lean body mass over time was a better appetite during chemotherapy.

We found an increase in body weight in the patient group of 1.1 kg during chemotherapy (from 72.0 kg ± 0.13 kg at baseline (T1) to 73.1 kg ± 0.23 kg shortly after chemotherapy (T2), which is in line with the results of our meta-analysis were we found a mean weight gain of 1.4 kg in women receiving a newer chemotherapy regime[8]. After chemotherapy (T3), body weight decreased to 72.7 kg ± 0.38 kg and was not longer significantly different from baseline. These findings on body weight are consistent with several other recent studies that also did not find substantial weight gain[13,14,28,41]. Older studies[5,9,15,19,42-46] tended to find increases in body weight, possible because those studies included other chemotherapy regimens.

Our results suggest that lean body mass increased during chemotherapy, but decreased to baseline values in the 6 months after chemotherapy. This increase in lean body mass during chemotherapy was unexpected, especially since physical activity decreased during chemotherapy compared to baseline values. Therefore, it is likely that the increase in lean body mass is not a change in muscle mass, but a change in body fluid. The findings from Pedersen[13] support this

suggestion, as they showed an increase in total body water, measured by BIA, 6 months after start of chemotherapy in breast cancer patients, which was normalized to baseline values after 12 months[13]. A possible explanation for fluid retention could be the use of a chemotherapy regime including docetaxel, since it is suggested that docetaxel can cause fluid retention[47]. Additionally, dexamethasone – which is frequently prescribed during chemotherapy - can cause fluid retention. In our study, we could not assess use of dexamethasone as medical records only contained information on prescription of this drug, but not on actual use.

Fat mass in the patient group was stable during chemotherapy and slightly but significantly increased in the 6 months after chemotherapy. However, over the whole study period, there was no differential change in fat mass between the patient and comparison group. Thus, it seems not possible to attribute the change in fat mass to the cancer treatment. This finding highlights the importance of including a comparison group. Without a comparison group, it could be concluded that women gain fat mass after chemotherapy treatment.

Our finding that younger age was associated with greater changes in body weight and fat mass are consistent with findings from others[1,10,15]. Other studies suggest that this may be related to menopausal status at diagnosis[1,3,13,14]. However, it is challenging to obtain reliable information on menopausal status[48], and since we only had self-reported data on menopausal status in our study, we decided to include age at diagnosis in our analysis.

Body weight and body composition were assessed using a DEXA-scan; for each participant all measurements were performed on the same scanner. Thus, although several scanners were used in this study, each participant was measured three times on the same scanner in the same hospital. Therefore, it was possible to assess changes over time within a person, although we cannot exclude that the type of scanner used, influenced the observed changes. In our study, we used body weight as assessed with the DEXA-scan, since it turned out to be logistically impossible to use validated scales to assess body weight. In a subgroup of 60 participants we measured body weight by scale and DEXA-scan on all three time points and showed that changes in body weight over time were not different based on scale measurement vs based on DEXA-scans.

In conclusion, we observed that in the period from start of chemotherapy until 6 months after the end of chemotherapy changes in body weight and body composition are minimal in women with breast cancer, and do not differ substantially from natural changes over time in women of a similar age without breast cancer. During chemotherapy we observed slight increases in body weight and body composition, however, 6 months after chemotherapy there were no differences between patients and women without cancer. This study does not confirm findings from others that fat mass and/or lean body mass change substantially during chemotherapy in breast cancer patients.

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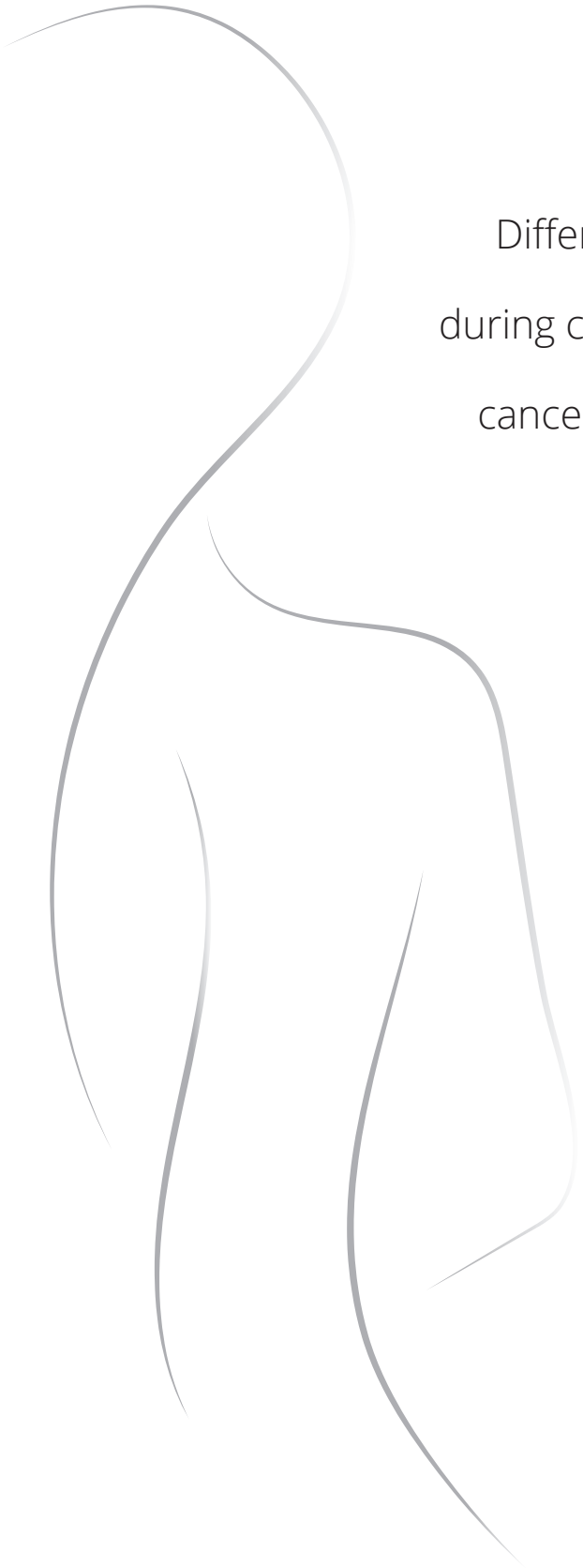

Chapter 5

Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer

Y.C. de Vries*,
M.M.G.A. van den Berg*,
J.H.M. De Vries,
S. Boesveldt,
J.Th.C.M. de Kruif,
N. Buist,
A. Haringhuizen,
M. Los,
D.W. Sommeijer,
J.H.N. Timmer-Bonte,
H.W.M van Laarhoven,
M. Visser,
E. Kampman,
R.M. Winkels

*Shared first authorship

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Abstract

Purpose: Breast cancer patients receiving chemotherapy often experience symptoms such as nausea, vomiting and loss of appetite that potentially affect dietary habits. This study assessed the intake of energy, macronutrients and food groups before and during chemotherapy in breast cancer patients compared with women without cancer, and determined the association between symptoms and energy and macronutrient intake.

Methods: This study included 117 newly diagnosed breast cancer patients scheduled for chemotherapy and 88 women without cancer. Habitual intake before chemotherapy was assessed with a food frequency questionnaire. Two 24h dietary recalls were completed on random days for each participant during the whole chemotherapy treatment for patients and within 6 months after recruitment for women without cancer. Shortly after the dietary recall, participants filled out questionnaires on symptoms.

Results: Before chemotherapy, habitual energy and macronutrient intake was similar for breast cancer patients and women without cancer. During chemotherapy, breast cancer patients reported a significantly lower total energy, fat, protein and alcohol intake than women without cancer, as shown by a lower intake of pastry and biscuits; cheese; legumes; and meat products. A decline in subjective taste perception, appetite, hunger, and experiencing a dry mouth, difficulty chewing, lack of energy and nausea were associated with a lower energy intake.

Conclusions: Symptoms induced by chemotherapy are associated with lower dietary intake, and manifested by a lower intake of specific food groups. To ensure an optimal dietary intake during chemotherapy, it is important to monitor nutritional status and symptom burden during chemotherapy in breast cancer patients.

Introduction

The majority of women with breast cancer is treated with chemotherapy[1]. Treatment with cytotoxic drugs is often accompanied with symptoms such as nausea, vomiting, loss of appetite, dry mouth and changes in taste or smell perception. These symptoms can be very disturbing and can significantly impact quality of life[2,3]. In types of cancer where the gastro-intestinal tract is affected, such as head and neck cancer, the impact of these symptoms on dietary intake and nutritional status is well established[4,5]. However, for breast cancer patients the experience of symptoms during cancer treatment may differ and the extent to which symptoms specifically affect dietary intake in breast cancer patients is less clear.

Previous studies that investigated whether dietary intake changed during chemotherapy in breast cancer patients are inconsistent in their findings. They either showed increases[6], decreases[7,8], or no changes[9-11] in energy intake during chemotherapy, possibly because different studies used different methods and different time points during the course of chemotherapy to assess dietary intake. Most studies in breast cancer patients assessed dietary intake only in the week prior to a next chemotherapy cycle, while dietary intake is suggested to vary during a cycle[12]. Most importantly, earlier studies did not compare dietary intake in breast cancer patients to a comparable group of women without breast cancer, limiting the possibility to assess whether changes in intake deviate from normal fluctuations in intake over time. Additionally, most studies are limited by only focussing on energy and macronutrient intake, and not on food items or food groups. Thereby it is unknown whether changes in dietary intake during chemotherapy are due to changes in intake of specific food groups.

There are studies that suggest that breast cancer patients gain weight during and after chemotherapy, which may be associated with an increased risk of comorbidities like cardiovascular disease and diabetes[13,14]. Therefore it is important to give breast cancer patients well-grounded advice on their lifestyle and dietary habits before, during and after treatment. Especially since breast cancer patients have expressed a need for dietary support during treatment with chemotherapy[15]; unmet supportive care needs in cancer patients are highest during treatment[16]. However, in order to give specific dietary advice it is important to first know

what the actual change in dietary intake of breast cancer patients is and which symptoms are associated with dietary changes during chemotherapy.

Therefore, the aim of this observational study was to assess the intake of energy, macronutrients and food groups before and during chemotherapy in breast cancer patients in comparison with a group of women without cancer, and to determine the association between the experience of specific symptoms and energy and macronutrient intake.

Materials and Methods

Participants

This study is part of an ongoing observational multi-centre study among breast cancer patients during chemotherapy and a comparison group of women of similar age without cancer (COBRA-study). Women with newly diagnosed, incident, stage I-IIIB, operable breast cancer, scheduled for 2nd or 3rd generation chemotherapy were compared with women without cancer of similar age (range within 2 years). Eligible patients were recruited by the staff of 11 participating hospitals prior to commencement of chemotherapy. The comparison group was recruited via the women with breast cancer, who were asked to distribute information about the study to female friends, acquaintances and colleagues. This approach was chosen to maximize the comparability of groups with respect to possible confounding factors, and thus to minimize the risk that other factors than chemotherapy influenced our findings on dietary intake. Women without cancer contacted the researchers if they were interested in participating in the study. All study participants needed to be at least 18 years old and be able to communicate in Dutch. Exclusion criteria were: history of cancer, previous treatment with chemotherapy, pregnancy or the intention to get pregnant during the study period, dementia or other mental conditions that made it impossible to comply with the study procedures. The protocol was approved by the Medical Ethical Committee of Wageningen University (ABR NL40666.081.12). All participants provided written informed consent before enrolment.

Measurements

Dietary intake

Upon recruitment, all participants filled out a food frequency questionnaire (FFQ) to assess habitual intake before chemotherapy (patient group) or start of the study (comparison group)[17,18]. During chemotherapy, actual dietary intake was assessed using two telephone-based 24h dietary recalls, because of the expected high day to day variation during chemotherapy. The recalls were planned on two random days during chemotherapy, during all weeks within a chemotherapy cycle and over all chemotherapy cycles administered. Recalls were planned between the day of the first chemotherapy infusion and three weeks after the last chemotherapy infusion. Women in the comparison group also completed two recalls, which were planned on two random days within 6 months after recruitment. This was a comparable time-frame, as current oncological guidelines for chemotherapy for breast cancer in the Netherlands encompass schemes which mostly take 4.5 to 6 months to complete. Randomization of the recall days was done for each participant separately. The two recalls were scheduled at least 7 days apart. If it was not possible to complete the recall on the scheduled day, a new day was planned randomly within 2 weeks. The 24h-recalls were performed using a standardized protocol and conducted by trained dietitians. The recalls were at least one week apart and were conducted both on week and weekend days. Dietary recall data were coded and entered, after which the intake of total energy, protein, carbohydrate, fat, alcohol and fibre were calculated in the computation module of Compl-eat™ using the Dutch food composition table 2013[19]. A data check was performed by the dietitians. The highest and lowest ten values for energy, macronutrients, and fruit and vegetables intake were checked for errors in coding or amounts. Food items were grouped into food groups for both the food frequency questionnaire and 24h dietary recall[19]. These food groups were: bread; cereal and cereal products; fruit; vegetables; legumes; nuts, seeds and snacks; soups; soy products and vegetarian products; pastry and biscuits; sugar, candy sweet toppings and sweet sauces; milk and dairy products; cheese; eggs; meat and meat products; and fish.

Symptoms

After being called for each 24h recall, participants were instructed to fill out questionnaires on sensory perception and experienced symptoms. The Appetite, Hunger feelings and Sensory

Perception (AHSP) questionnaire was used to assess self-judgement of taste, smell and appetite[20]. The questionnaire consisted of 29 questions answered on a 5 point Likert scale, concerning four categories; taste (8 items, score range 8-40), smell (6 items, range 6-30), appetite (6 items, range 6-30) and hunger (9 items, range 9-45). An example of a question for taste was: In former days the taste of food was: 1. much better than nowadays, 2. better than nowadays, 3. the same as nowadays, 4. worse than nowadays, 5. much worse than nowadays. For the patient group, 'former days' was referenced as the situation before chemotherapy and for the comparison group as the situation one year ago. A higher score corresponds to a more positive judgement about current taste and smell perception, appetite and hunger. The severity of 13 additional symptoms was assessed: pain; dry mouth; feeling depressed; thick saliva; diarrhoea; sore mouth; lack of energy; nausea; difficulty chewing; difficulty swallowing; anxiety; constipation and vomiting. For each symptom the question was asked: 'How often have you experienced this symptom during the past three days?', scored on a 5 point Likert scale, ranging from 1="not at all" to 5="a lot". If participants did not answer the symptoms questionnaires within 3 days after complete the 24h dietary recall, we did not include their data in the analyses. In total, we collected n=274 recalls from patients and n=205 recalls from women without breast cancer. A number of n=205 recalls from breast cancer patients and n=152 recalls from women without cancer were used in the analyses in this paper. Excluding participants who did not complete the questionnaires within 3 days from analysis did not significantly influence the results on energy and macronutrient intake.

Demographics and medical information

All participants filled out a baseline questionnaire for demographic information, including age, smoking status and educational level. Information on stage of cancer at diagnosis and treatment were obtained from reviewing patients' medical records. Dates of chemotherapy cycles were compared with the dates of the 24h-recalls to classify the recalls into the week within a chemotherapy cycle and to the number of cycles that was administered at the date of the 24h recalls.

Data analysis

Population characteristics were described as medians with interquartile range (IQR) or percentages of the patient and comparison group separately. To assess differences in the population characteristics between the groups, the Mann-Witney U-test was used for continuous data and the Chi Square test for categorical data. Differences in dietary intake at study onset (FFQ) between the women with and without breast cancer were analysed with Linear Regression. Mixed Model analysis was used to assess differences in energy, macronutrient and food group intake between the patient and comparison group. For the analysis of differences in dietary intake within a chemotherapy cycle for patients receiving a three weekly scheme of chemotherapy, recalls were classified according to the week within a chemotherapy cycle a 24h-recall was administered (week 1, week 2 or week 3) and to the number of cycles administered. Patients with weekly chemotherapy cycles were excluded from this analysis (n=22 recalls). Mixed models were also used to assess the association between symptoms and energy intake. Interactions between each symptom and group (patient and comparison group) were evaluated to test whether associations between symptoms and energy intake were different between the two groups. For significant interactions (p-value ≤0.1), stratified results for patients and the comparison group are shown. For symptoms with a significant association with energy intake, data was also analysed for the macronutrients protein, carbohydrates and fat. Covariates considered as potential confounders were included in the regression and mixed models analyses based on literature and change of regression coefficient. Variables that changed the regression coefficient ≥ 10% in the adjusted model compared to the crude model were included in the final model. Final regression and mixed models analyses were adjusted for: age at inclusion, BMI at inclusion, education level, and smoking status at inclusion. Statistical analyses were performed using SPSS, version 21 (SPSS inc. Chicago, IL). A p-value < 0.05 was considered as statistically significant.

Results

Patient characteristics

Data were collected for 117 breast cancer patients and 88 women in the comparison group, see table 5.1. BMI was higher in women with breast cancer than in women without breast cancer. In the patient group, fewer women had a high educational level than in the comparison group. There were no differences for age, smoking status and menopausal status between the groups. The majority of the breast cancer patients had a stage 2 tumour, and received adjuvant chemotherapy combining taxanes and anthracyclines.

Table 5.1. Demographic and clinical characteristics of the patient and comparison group included in the study.

Characteristic	Comparison group (n=88)	Patient group (n=117)
Demographics		
Age, years (median, IQR)	53.5 (46.1 – 60.9)	51.0 (46.8 – 55.3)
Education level (n, %) *		
Low	4 (4.5)	12 (10.4)
Medium	18 (20.5)	35 (30.4)
High	66 (75.0)	68 (59.1)
Lifestyle		
BMI, kg/m^2 (median, IQR) *	23.8 (22.1 – 26.7)	25.2 (22.3 – 28.4)
Smoking status (n, %)		
Current	9 (10.2)	21 (18.1)
Former	40 (45.5)	49 (42.2)
Never	39 (44.3)	46 (39.7)
Medical profile		
Tumor Stage (n, %)		
I		25 (21.4)
II		70 (59.8)
III		22 (18.8)
Adjuvant chemotherapy (n, %)		68 (58.1)
Neo adjuvant chemotherapy (n, %)		49 (41.9)
Chemotherapy regimen (n, %)		
Taxanes only		4 (3.4)
Anthracyclines only		4 (3.4)
Taxanes + Anthracyclines		109 (93.2)

Abbreviations: IQR, Interquartile range;
Missings per variable : education, 2; smoking, 1.
* $P<0.05$

Dietary intake at study onset

At study onset, mean energy, protein, fat and carbohydrate intakes were similar between the patient and comparison group as assessed with a food frequency questionnaire (table 5.2).

Women with breast cancer reported to consume less alcohol than women in the comparison group. Intake for the various food groups was similar between the two groups, with the exception of cheese intake, which was slightly higher in breast cancer patients compared to the women without cancer.

Dietary intake during chemotherapy

In total, 357 recalls were collected, 205 in the patient group and 152 in the comparison group. During chemotherapy, breast cancer patients had a significantly lower energy intake than the women without cancer as assessed with 24h dietary recalls, 1779 ± 56 vs 1993 ± 68 kcal (table 5.3). Breast cancer patients reported a significant lower absolute intake of protein, fat, and alcohol, but not of carbohydrates and fibre than women without cancer. Expressed as energy percentages, during chemotherapy women with breast cancer consumed relatively more energy from carbohydrates and less energy from alcohol compared to women without cancer.

During chemotherapy, women with breast cancer consumed less energy from the food groups legumes; pastry and biscuits; cheese; and meat than the women without cancer (table 5.4). The intake of other food groups: bread; cereal and cereal products; fruit; vegetables; nuts, seeds and snacks; soups; soy and vegetarian products; sugar, sweets, sweet toppings and sweet sauces; milk and dairy products; cheese; eggs; and fish was similar between breast cancer patients during chemotherapy and women without cancer. Results expressed in grams/day can be found in Supplementary table 5.1. The main sources of total protein, fat and carbohydrate intake were similar for the patient and the comparison group. The main sources of protein intake were meat, bread and milk and dairy products. For fat the main sources were fats, oils and savoury sauces, cheese and meat, Carbohydrates came mostly from the food groups bread, alcoholic and non-alcoholic drinks, milk and dairy products and fruit.

Dietary intake in the patient group was lower compared to the women without cancer in all three weeks after chemotherapy was administered, and was lowest in each first week However, there were no statistically significant differences in energy and macronutrient intake between the first, second and third week within a chemotherapy (Supplementary table 5.2). In addition, there was no association between dietary intake and the number of chemotherapy cycles administered.

Table 5.2. Habitual intake of energy, macronutrients and food groups for the patient and comparison group (mean ± SE) and differences in intake between the groups at study onset, assessed by a food frequency questionnaire.

	Intake in kcal (mean ± SE)		
	Comparison group (N=88)	**Patient group (N=114)**	**Difference[a] [95% CI]**
Energy	2069 ± 69.2	2070 ± 59.7	1 [-181 ; 184]
Protein	318 ± 10.1	315 ± 8.7	-3 [-30 ; 24]
Carbohydrate	859 ± 31.3	870 ± 27.0	11 [-71 ; 93]
Fat	761 ± 32.3	779 ± 27.8	18 [-67 ; 103]
Alcohol*	75 ± 7.5	51 ± 6.5	-24 [-44 ; -4]
Fibre	46 ± 1.6	45 ± 1.4	-1 [-5 ; 3]
Food groups			
Bread	256 ± 16.7	256 ± 14.4	0 [-44 ; 44]
Cereal and cereal products	139 ± 10.9	131 ± 9.4	-8 [-37 ; 21]
Fruit	134 ± 8.3	118 ± 7.2	-16 [-37 ; 7]
Vegetables	50 ± 3.5	53 ± 3.0	3 [-6 ; 12]
Legumes	10 ± 1.6	11 ± 1.4	1 [-4 ; 5]
Nuts, seeds and snacks	168 ± 15.7	146 ± 13.5	-22 [-63 ; 19]
Soups	24 ± 3.3	22 ± 2.8	-2 [-11 ; 6]
Soy products and vegetarian products	18 ± 5.3	16 ± 4.5	-2 [-15 ; 12]
Pastry and biscuits	119 ± 11.3	136 ± 9.7	17 [-13 ; 47]
Sugar, candy, sweet toppings and sweet sauces	110 ± 10.6	120 ± 9.2	10 [-18 ; 38]
Milk and dairy products	195 ± 13.9	173 ± 12.0	-22 [-58 ; 15]
Cheese*	105 ± 13.8	145 ± 11.9	40 [3 ; 76]
Eggs	25 ± 2.6	24 ±2.3	-1 [-8 ; 6]
Meat, meat products and poultry	153 ± 9.3	159 ± 8.0	6 [-19 ; 30]
Fish	36 ± 3.1	29 ± 2.7	-7 [-15 ; 11

[a] Adjusted for age, BMI, education level, smoking status
* p <0.05

Table 5.3. Energy and macronutrient intake in kcal and energy percentages (en%) for the breast cancer patients during chemotherapy and comparison group during follow up (mean ± SE) and the differences in intake between the groups.

	Intake in kcal (mean ± SE)		
	Comparison group	**Patient group**	**Difference[a] [95% CI]**
Energy*	1993 ± 68.3	1779 ± 55.7	-214 [-353 ; -76]
Protein*	313 ± 10.7	270 ± 8.8	-43 [-64 ; -21]
Carbohydrate	844± 34.4	815± 28.0	-29 [-99 ; 41]
Fat*	734 ± 32.0	633± 26.1	-101 [-166 ; -37]
Alcohol*	54 ± 9.4	17 ± 7.7	-37 [-57 ; -19]
Dietary fibre	38 ± 1.8	35 ± 1.4	-3 [-7 ; 1]
	Intake in en% (mean ± SE)		
Protein	16.3 ± 0.45	15.5 ± 0.37	-0.8 [-1.6 ; 0.2]
Carbohydrate*	41.9 ± 1.0	46.2 ± 0.82	4.3 [2.2 ; 6.3]
Fat	36.6 ± 0.85	35.0 ± 0.70	-1.6 [-3.4 : 0.1]
Alcohol*	2.8 ± 0.47	0.8 ± 0.38	-2.0 [-2.9 ; -1.0]
Dietary fibre	2.0 ± 0.09	2.0 ± 0.07	0.0 [-0.1 ; 0.2]

[a] Adjusted for age, BMI, education level, smoking status

* $p < 0.05$

Table 5.4. Intake per food group for the breast cancer patients during chemotherapy and comparison group during follow up (mean ± SE) and the differences in intake between the groups in kcal.

	Intake in kcal* (mean ± SE)		
	Comparison group	**Patient group**	**Difference [95% CI][a]**
Bread	332 ± 39.5	291 ± 37.2	-41 [-81 ; 2]
Cereal and cereal products	68 ± 29.4	67 ± 27.7	-1 [-32 ; 31]
Fruit	98 ± 26.5	86 ± 24.9	-121 [-40 ; 16]
Vegetables	41 ± 9.4	33 ± 8.9	-8 [-17 ; 3]
Legumes*	136 ± 39.2	83 ± 36.9	-53 [-95 ; -12]
Nuts seeds and snacks	7 ± 11.8	9 ± 11.1	2 [-11 ; 14]
Soups	35 ± 28.5	22 ± 26.8	-13 [-43 ; 18]
Soy products and vegetarian products	29 ± 14.9	31 ± 14.0	2 [-14 ; 18]
Pastry and biscuits*	131 ± 36.6	84 ± 34.4	-47 [-86 ; -8]
Sugar, candy, sweet toppings, and sweet sauces	90 ± 28.7	86 ± 27.0	-4 [-34 ; 26]
Milk and dairy products	164 ± 36.6	170 ± 34.5	6 [-33 ; 44]
Cheese*	140 ± 22.4	112 ± 21.1	-28 [-52 ; -4]
Eggs	35 ± 9.1	39 ± 8.6	4 [-6 ; 14]
Meat, meat products and poultry*	190 ± 31.8	150 ± 29.9	-40 [-74 ; -6]
Fish	25 ± 22.3	42 ± 20.95	17 [-8 ; 40]

[a] Adjusted for age, BMI, education level, smoking status

* $p < 0.05$

Symptoms

During chemotherapy, the patient group scored significantly lower on their self-reported taste, smell, appetite and hunger, compared to the women without cancer (table 5.5). Furthermore, breast cancer patients undergoing chemotherapy experienced more often anxiety, dry mouth, constipation, feeling depressed, thick saliva, diarrhoea, sore mouth, lack of energy, nausea, difficulty chewing and difficulty swallowing than women in the comparison group (table 5.6). Scores were not different for the symptoms pain and vomiting between the patient and the comparison group. Only 3 women with breast cancer and 1 woman without breast cancer reported vomiting as a symptom they experienced that day, therefore vomiting was not analysed for its association with energy intake.

Table 5.5. Taste, smell, appetite and hunger scores from AHSP questionnaire for the breast cancer patients during chemotherapy and comparison group during follow up (mean ± SE) and the association of AHSP categories with energy intake (kcal). Higher scores indicate a more positive self-judgement on the categories of the questionnaire. β for energy intake is the difference in energy intake (kcal) per 1 unit higher score within ASHP category.

		Score questionnaire (mean ± SE)			
Category	Range	Comparison group	Patient group	Difference	Estimate (β) for energy intake (kcal)[a] [95% CI]
Taste	8-40	30.9 ± 0.71	22.0 ± 0.57	-8.9* [-10.4 ; -7.5]	16.4* [7.0 ; 25.8]
Smell	6-30	23.3 ± 0.42	20.6 ± 0.42	-2.7* [-3.7 ; -1.8]	11.9 [-5.0 ; 28.7]
Appetite	6-30	24.7 ± 0.40	18.7 ± 0.50	-6.0* [-7.0 ; -5.0]	26.5* [14.4 ; 38.5]
Hunger	9-45	38.3 ± 0.70	32.5 ± 0.70	-5.8* [-7.4 ; -4.3]	24.5* [15.1 ; 33.9]

[a] Adjusted for age, BMI, education level, smoking status
* p <0.05

Symptoms and dietary intake

A higher self-judgement of taste perception, better appetite and more hunger were significantly associated with a higher energy intake (table 5.5). Self-judgement of smell was not significantly associated with energy intake.

Having a dry mouth, lack of energy, nausea and having difficulty chewing were significantly associated with a lower energy intake (table 5.6). The associations between anxiety and energy intake and between constipation and energy intake were different for the patient and the comparison group (interaction anxiety p=0.02, constipation p=0.03): anxiety was not associated with energy intake in breast cancer patients, while it was associated with a lower energy intake in the comparison group. Constipation was associated with a higher energy intake in the patient group and with a lower energy intake in the comparison group, but these associations were not statistically significant (table 5.6).

For the symptoms that were significantly associated with energy intake, we additionally assessed whether those symptoms were associated with protein, carbohydrate and fat intake. Briefly, those associations were in the same direction as how the intake of macronutrients differed during chemotherapy between the patients and the comparison group: symptoms were associated with a lower protein and fat intake, and not associated with the intake of carbohydrates (Supplementary table 5.3).

Table 5.6. Results of the symptom questionnaire for the breast cancer patients during chemotherapy and comparison group during follow up (mean ± SE) and the association between symptoms and energy intake (kcal). Symptom severity was assessed on a 5 point Likert scale (1=not at all, 5=a lot). β for energy intake indicates the difference in energy intake (kcal) per 1 unit higher score in the symptom.

	Score questionnaire (mean ± SE)			
Symptom	Comparison group	Patient group	Difference	Estimate (β) for energy intake (kcal)[a] [95%CI]
Pain	1.6 ± 0.13	1.9 ± 0.11	0.3 [-0.005 ; 0.520]	54.2 [-2.8 ; 111.2]
Dry mouth	1.3 ± 0.15	2.9 ± 0.12	1.6 [1.3 ; 1.9]*	-47.1* [-92.5 ; -1.8]
Depressed	1.3 ± 0.1	1.6 ± 0.08	0.3 [0.1 ; 0.5]*	5.4 [-68.4 ; 79.1]
Thick saliva	1.1 ± 0.12	1.9 ± 0.10	0.8 [0.6 ; 1.1]*	-56.3 [-114.1 ; 1.5]
Diarrhoea	1.0 ± 0.09	1.5 ± 0.07	0.5 [0.2 ; 0.6]*	-3.1 [-75.9 ; 69.6]
Sore mouth	1.3 ± 0.13	2.2 ± 0.11	0.9 [0.7 ; 1.2]*	-35.7 [-86.0 ; 14.6]
Lack of energy	1.6 ± 0.14	3.3 ± 0.12	1.7 [1.5 ; 2.0]*	-55.5* [-99.0 ; -12.1]
Nausea	1.1 ± 0.1	1.7 ± 0.08	0.6 [0.4 ; 0.8]*	-77.7* [-139.4 ; -16.0]
Difficulty chewing	1.1 ± 0.09	1.5 ± 0.07	0.4 [0.2 ; 0.6]*	-102.6* [-180.3 ; -24.9]
Difficulty swallowing	1.1 ± 0.08	1.5 ± 0.06	0.4 [0.2 ; 0.6]*	-33.6 [-117.1 ; 49.8]
Constipation[b]	1.3 ± 0.12	1.8 ± 0.09	0.5 [0.2 ; 0.7]*	
Constipation control				-103.3 [-228.8 ; 22.3]
Constipation patient				42.1 [-34.1 ; 118.5]
Anxiety[b]	1.2 ± 0.08	1.5 ± 0.07	0.3 [0.1 ; 0.4]*	
Anxiety Control				-208.7* [-384.1 ; -33.3]
Anxiety Patient				83.1 [-18.2 ; 184.5]
Vomiting[c]	1.0 ± 0.04	1.1 ± 0.03	0.04 [-0.04 ; 0.12]	

a Adjusted for age, BMI, education level, smoking status
b For anxiety and constipation significant interactions were found on the association with energy intake, therefore stratified results are shown.
c For vomiting only 1 control and 3 patients reported a score of 2 or higher on the questionnaire, therefore this symptom was not analysed for the association with energy intake.

Discussion

To date, this is the largest study that examined energy, macronutrient and food group intake in breast cancer patients during chemotherapy compared to a group of women without cancer. We showed that breast cancer patients had a significantly lower energy intake during chemotherapy compared with a group of women without cancer. Since habitual intake of breast cancer patients before start of chemotherapy was comparable to the women without cancer in our study, we can assume that the differences found between the groups were mostly due to the consequences of chemotherapy. These findings are in accordance with two other studies that observed a lower energy intake in breast cancer patients during chemotherapy compared to before chemotherapy[7,8]. Only one previous study, published in 1987, suggested a higher dietary intake during chemotherapy in breast cancer patients compared with controls6. However, that study had a control group which already had a lower intake at baseline, limiting the reliability of those conclusions.

The lower energy intake that we observed during chemotherapy was not caused by a lower intake of all macronutrients. The intakes of fat, protein and alcohol were lower during chemotherapy in breast cancer patients than in women without cancer, while intakes of carbohydrates and dietary fibre were similar. The lower protein and fat intake can be explained by the food groups that were consumed less during chemotherapy: meat and cheese are mostly high in protein and fat, and may thereby partially account for the different intakes of macronutrients. Habitual alcohol intake was lower in breast cancer patients before chemotherapy than women without cancer, and the intake remained lower during chemotherapy. As alcohol is a known risk factor for breast cancer[21], a higher or comparable alcohol intake could be expected in the patient group compared wo the women without cancer. Possibly, breast cancer patients underreported their alcohol intake due to social desirability bias. However, it is also possible that breast cancer patients changed their dietary habits due do cancer diagnosis. Cancer diagnosis has been referred to as a 'teachable moment' for lifestyle changes and may motivate patients to change their dietary habits[22].

Patients in our study experienced a variety of symptoms during chemotherapy, but not all were

associated with energy intake. Specifically, the symptoms of lower self-reported taste, lower appetite, less hunger, dry mouth, lack of energy, nausea and difficulty chewing were associated with a lower energy intake. These symptoms are known to limit the enjoyment of eating as they make eating more difficult. It is thus not surprising that they have been previously related to a lower energy intake[4,23]. Interestingly, self-judgement of taste was significantly associated with energy intake, but self-judgement of smell was not, while smell function is generally recognized as an important factor for food intake[24]. We must consider that humans are generally not well able to rate their own smell sensitivity[25]. Therefore, we cannot exclude that reduced smell function influences energy intake. The experience of symptoms does not only have an effect on dietary intake, symptoms also negatively impact quality of life[26]. Therefore it is important to monitor symptoms during chemotherapy, and to treat symptoms where possible. Furthermore, given the associations of symptoms with dietary intake, it is important to monitor nutritional status to ensure an adequate intake of energy and nutrients during chemotherapy.

In addition to experienced symptoms, changed preferences for foods may be related to the changed food choices we observed during chemotherapy. Aversions for meat are commonly reported during chemotherapy[27,28], and may thereby underlie the lower intake of this food group that we observed in breast cancer patients during chemotherapy compared to the women without cancer. However, research on food preferences during chemotherapy is mostly anecdotal and scarcely measured quantitatively and should be taken into account in future studies.

Studies suggest that breast cancer patients gain weight during and after chemotherapy[13,14]. To date, it is not clear which factors underlie these weight changes. However, our study does not suggest nutritional intake as a contributing factor for this weight gain, as we observe a decreased energy intake of patients during chemotherapy. However, breast cancer patients may have a lower energy requirement, as physical activity may be lower[9,29]. Additionally, reductions in resting energy expenditure have been reported during and after chemotherapy[13,14.] Therefore, studies assessing weight change during chemotherapy should take changes in dietary intake, physical activity and resting energy expenditure into account to assess the contribution of these factors on weight change.

Previous studies investigating dietary intake during chemotherapy in breast cancer patients were heterogeneous in the time points dietary intake was assessed. Mostly, it was assessed the week before a next cycle would be administered. In our study, we deliberately chose to assess dietary intake at random days during the full cycle of chemotherapy, thereby capturing the full variation in dietary intake over chemotherapy. Although there were no significant differences between the weeks within chemotherapy cycles, there was variation within the weeks; dietary intake was lowest in the first week after a cycle was administered. This renders the importance to take into account all weeks within chemotherapy cycles to give a correct representation of dietary intake during chemotherapy.

It cannot be excluded that differential reporting of dietary intake between patients and the comparison group influenced the results of our study. Differential reporting may be influenced by differences in BMI[30]. BMI was slightly higher in the patient group than the comparison group at the start of our study. As persons with higher BMI tend to underestimate dietary intake, the patient group may have underestimated their intake, explaining the difference in intake between women with breast cancer and women without cancer observed during chemotherapy. However, habitual intake was similar between patients and the comparison group at baseline and analyses were adjusted for BMI. Therefore, we do not expect that differential reporting substantially influenced our results.

In conclusion, our study is the largest study to date showing that breast cancer patients have a lower dietary intake during chemotherapy, which is expressed in a lower intake of specific food groups. The lower intake was associated with specific symptoms. These finding can guide clinicians to inform patients about the potential impact of chemotherapy and related symptoms on dietary intake and to ensure an adequate intake of energy and nutrients during chemotherapy.

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Supplementary table 5.1. Intake per food group for the breast cancer patients during chemotherapy and comparison group during follow up (mean ± SE) and the differences in intake between the groups in grams.

	Intake in gram (mean ± SE)		
	Comparison group	**Patient group**	**Difference [95% CI][a]**
Bread	124 ± 15.3	110 ± 14.4	-14 [-31 ; 2]
Cereal and thickeners	35 ± 17.4	37 ± 16.4	2 [-16 ; 21]
Fruit	131 ± 34.8	125 ± 32.8	-6 [-43 ; 31]
Vegetables	152 ± 29.1	125 ± 27.4	-27 [-58 ; 4]
Legumes*	33 ± 10.4	19 ± 9.8	-14 [-25 ; -3]
Nuts seeds and snacks	14 ± 18.1	8 ± 17.1	-6 [-25 ; 13]
Soups	25 ± 19.5	21 ± 18.4	-4 [-25 ; 17]
Soy products and vegetarian products	76 ± 29.9	77 ± 28.1	1 [-31 ; 33]
Pastry and biscuits*	40 ± 11.2	25 ± 10.5	-15 [-27 ; -3]
Sugar, candy, sweet toppings, and sweet sauces	22 ± 6.4	21 ± 6.0	-1 [-7 ± 6]
Milk and dairy products	260 ± 54.8	247 ± 51.7	-13 [-70 ; 44]
Cheese*	39 ± 6.5	31 ± 6.1	-8 [-15 ; -1]
Eggs	27 ± 6.6	30 ± 6.2	3 [-5 ; 9]
Meat, meat products and poultry*	92 ± 14.4	76 ± 13.6	-16 [-32 ; -1]
Fish	18 ± 12.4	20 ± 11.7	2 [-11 ± 16]

[a] Adjusted for age, BMI, education level, smoking status
* p <0.05

Supplementary table 5.2. Energy and macronutrient intake per week within the chemotherapy cycle. Week 1: n=90 recalls, week 2: n= 60 recalls, week 3: n=42 recalls.

	Intake in kcal* (mean ± SE)	Difference [95% CI][a]
Energy		
Week 1	1751 ± 74.1	Ref
Week 2	1883 ± 84.0	132 [-54 ; 318]
Week 3	1861 ± 95.6	110 [-96 ; 315]
Protein		
Week 1	267 ± 12.6	Ref
Week 2	286 ± 14.4	19 [-14 ; 52]
Week 3	283 ± 16.5	16 [-21 ; 53]
Fat		
Week 1	621 ± 34.2	Ref
Week 2	665 ± 39.0	43 [-44 ; 130]
Week 3	671 ± 44.3	50 [-47 ; 146]
Carbohydrate		
Week 1	816 ± 38.1	Ref
Week 2	863 ± 42.9	47 [-45 ; 139]
Week 3	847 ± 48.1	30 [-71 ; 131]

[a] Adjusted for age, BMI, education level, smoking status

Supplementary table 5.3. The association of AHSP and symptom categories and intake of protein, carbohydrate and fat (kcal) for the categories that were significantly associated with energy intake.

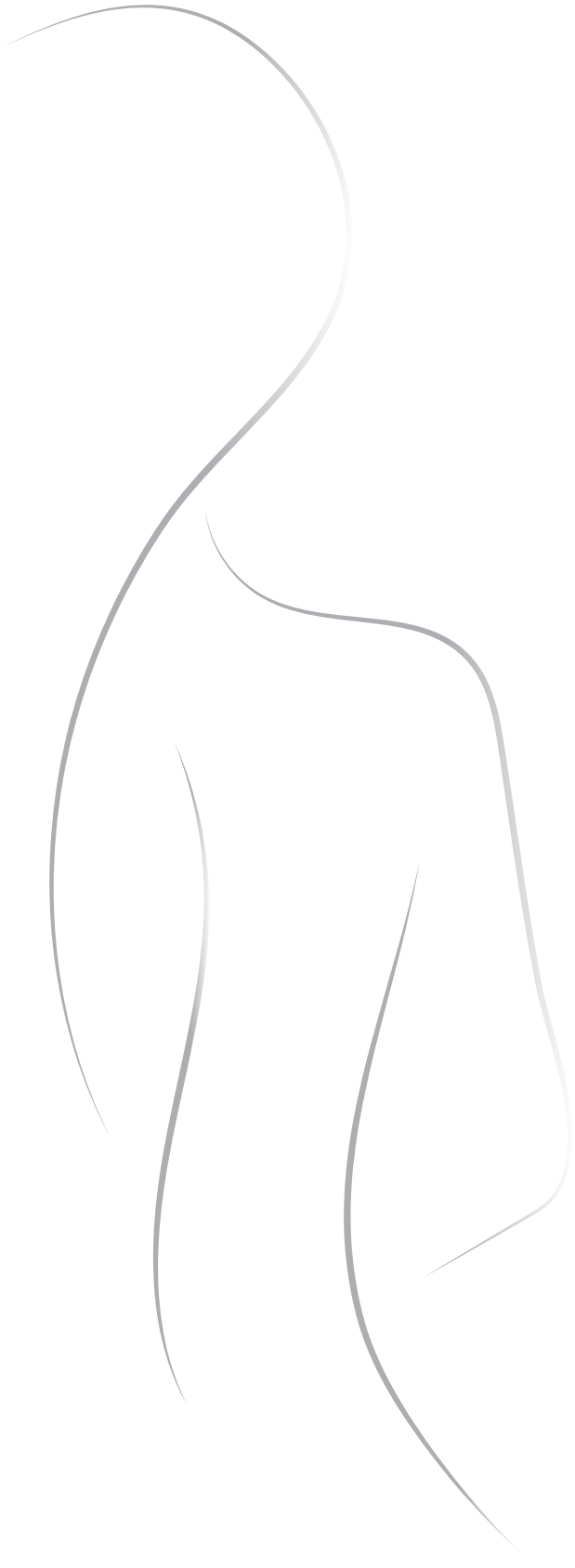
Symptom	Estimate (β) for protein intake (kcal)[1] [95%CI]	Estimate (β) for carbohydrate intake (kcal)[a] [95%CI]	Estimate (β) for fat intake (kcal)[a] [95%CI]
Taste[b]	3.5* [2.0 ; 5.0]	2.6 [-2.1 ; 7.3]	7.7* [3.3 ; 12.1]
Appetite[b]	5.1* [3.1 ; 7.1]	5.5* [0.6 ; 11.5]	12.6* [6.9 ; 18.3]
Hunger[b]	4.2* [2.7 ; 5.7]	8.5* [3.8 ; 13.2]	10.2* [5.7 ; 14.7]
Dry mouth[c]	-8.0* [-15.7; -0.4]	-7.9 [-30.3; 14.5]	-21.0 [-42.6; 0.7]
Lack of energy[c]	-12.2* [-19.5 ; -4.8]	-12.0 [-33.5 ; 9.5]	-22.6* [-43.4 ; -1.8]
Nausea[c]	-11.1* [-21.9 ; -0.2]	-8.6 [-39.1 ; 21.9]	-42.4* [-72.3 ; -12.5]
Difficulty chewing[c]	-14.9* [-28.4 ; -1.3]	-20.2 [-58.6 ; 18.2]	-61.6* [-99.0 ; -24.2]

[a] Adjusted for age, BMI, education level, smoking status

[b] β for macronutrient intake is the difference in macronutrient intake (kcal) per 1 unit higher score within ASHP category.

[c] β for macronutrient intake indicates the difference in macronutrient intake (kcal) per 1 unit higher score in the symptom.

*p < 0.05



Chapter 6

General discussion

This thesis aims to assess among stage I-IIIB breast cancer patients:

1. the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy.
2. potential changes in body weight and body composition during and after chemotherapy compared to changes in age-matched women without cancer in the same time period.
3. dietary intake during chemotherapy compared to age-matched women without cancer in the same time period.

After summarizing the main findings of this thesis, methodological considerations including comparison with other studies and changes in breast cancer care will be discussed. This will be followed by the final conclusion and implications for clinical practice and future research.

Main findings

Pre-treatment body composition and dose-limiting toxicities during chemotherapy

The first aim of this thesis was to assess the association between pre-treatment body weight and body composition and dose-limiting toxicities during chemotherapy. We assessed body weight and body composition before chemotherapy in the COBRA-study by Dual Energy X-ray Absorptiometry (DEXA)-scan and obtained information regarding toxicities during chemotherapy from medical records (chapter 2). Results of our study showed that a higher BMI and a higher fat mass (kg and percentage) are associated with an increased risk of dose-limiting toxicity, while lean body mass (kg) is not associated with risk of toxicities. This suggests that total fat mass determines the risk of dose-limiting toxicities during chemotherapy in breast cancer patients.

Changes in body weight and body composition during chemotherapy

The second aim of this thesis was to assess changes in body weight and body composition during chemotherapy. We assessed this using two methods; a meta-analysis and analyses within the COBRA-study (chapter 3 and 4).

Our meta-analysis (chapter 3), included 25 papers, showed an overall body weight gain of 2.7 kg (95% CI: 2.0-3.3) during chemotherapy in breast cancer patients. Meta-regression showed that studies including women treated with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimes reported a greater weight gain than studies including only women treated with newer, anthracycline and/or taxane based regimes. Body weight gain was also more pronounced in women who participated in studies that were published before 2000 than in those published after 2000.

The results of the COBRA-study (chapter 4), in which we prospectively followed changes in body weight and body composition during chemotherapy and 6 months after chemotherapy showed that women with breast cancer on average gained 1.1 kg body weight from baseline to shortly after chemotherapy. This was similar to the 1.4 kg body weight gain we found in a sub-analysis of our meta-analysis of studies including only women treated with newer chemotherapy regimes. We also showed that 6 months after chemotherapy body weight in the patient group was not different from baseline body weight. Women in the comparison group had no significant changes in body weight and body composition during the study period.

We showed that patients increased their lean body mass (kg) from baseline to shortly after chemotherapy. However, 6 months after chemotherapy lean mass had returned to baseline values and there were no differences in fat mass (kg) between the patient group and the comparison group of women without cancer. This suggests that the increase in lean body mass was only temporary.

From baseline to shortly after chemotherapy breast cancer patients had a stable fat mass. Six months after chemotherapy fat mass slightly, yet significantly, increased compared to baseline and compared to the period shortly after chemotherapy. Fat mass did not significantly differ over time between patients and women without cancer and there were no differences in fat mass between the two groups at all three time points.

Differences in dietary intake during chemotherapy

A third aim of this thesis was to assess differences in dietary intake during chemotherapy between women with breast cancer and a comparison group of women without cancer. Again we assessed this within the COBRA-study, using a Food Frequency Questionnaire (FFQ) to assess usual dietary intake before chemotherapy and twice utilizing a 24-hr dietary recall to assess actual dietary intake at two random days during chemotherapy among patients and twice during the same time frame among women in the comparison group (chapter 5).

Before the start of chemotherapy, women with breast cancer had a similar energy and macronutrient intake as women in the comparison group. During chemotherapy, women with breast cancer showed a lower intake of energy, total fat, total protein and alcohol than women without cancer, while there was no difference in total carbohydrate intake between the groups. The lower intake of energy, total fat and total protein was explained by a lower intake of pastry and biscuits, cheese, legumes, and meat products.

We assessed within the COBRA-study whether dietary intake before chemotherapy, eating style (restrained, emotional, external), or appetite, taste, and smell during chemotherapy were associated with greater changes in body weight, fat mass, and lean body mass over time (chapter 4). A higher score on appetite during chemotherapy was associated with greater changes in body weight, fat mass, or lean body mass over time. We showed that a younger age was associated with greater changes in body weight and fat mass over time, but not with changes in lean body mass over time. In addition, an ER-receptor negative tumour was associated with greater changes in body weight over time, but not with changes in fat mass or lean body mass over time (chapter 4). Baseline dietary intake, eating style, and taste and smell during chemotherapy were not associated with changes in body weight or body composition over time.

Summarizing, pre-treatment body composition (e.g. fat mass) is associated with dose-limiting toxicities during chemotherapy. Body weight gain during chemotherapy appears to be mainly an increase in lean body mass and decreased in the 6 months after chemotherapy. Habitual dietary intake before start of chemotherapy is not associated with changes in body weight and

body composition over time. A higher appetite during chemotherapy is associated with greater changes in body weight and body composition over time. A younger age is associated with greater changes in body weight and fat mass over time, but not with changes in lean body mass over time. An ER-receptor negative tumour is associated with greater changes in body weight over time, but not with changes in body composition over time. During chemotherapy, breast cancer patients have a lower intake of energy, total fat, and total protein compared to age-matched women without cancer in the same time period, which could be explained by a lower intake of pastry and biscuits, cheese, legumes, and meat products.

Methodological considerations including comparison with other studies

When interpreting these results and comparing the results with other studies, it is important to take into account methodological considerations. In this paragraph the internal and external validity of the COBRA-study will be discussed as compared to other studies.

Internal validity

This section about the internal validity consists of four parts including: study design, information error and bias, confounding, and selection error and bias. Each part will be discussed separately.

Study design

We conducted a prospective study among stage I-IIIB breast cancer patients treated with chemotherapy and compare their results with a comparison group of women without cancer of similar age during the same time period. Most published studies of changes in body weight and body composition during chemotherapy in breast cancer patients only included women treated with adjuvant chemotherapy[1-29]. Because the number of patients treated with neo-adjuvant chemotherapy is increasing, we decided to include both patients receiving adjuvant and neo-adjuvant chemotherapy. As a consequence of this inclusion of adjuvant and neo-adjuvant treated patients, participants were in different phases of breast cancer treatment at the moments of measurement within the COBRA-study, see figure 6.1.

Because neo-adjuvant chemotherapy starts shortly after diagnosis, the first moment of measurement had often be postponed from before the first cycle of chemotherapy to during the first cycle of chemotherapy. This could have influenced our baseline results on body weight, body composition, dietary intake, and physical activity, since minor changes in body composition could have occurred within the first cycle of chemotherapy and it could be more difficult to recall the situation before start of chemotherapy when patients are already receiving chemotherapy. For patients treated with adjuvant chemotherapy, body weight, body composition, physical activity and dietary intake may have been affected by the preceding surgery and/or radiotherapy. It is also possible that the different phases of treatment after chemotherapy had an influence on body weight and body composition. However, we do not expect that including patients treated with adjuvant and neo-adjuvant chemotherapy changed our conclusion, because associations between pre-chemotherapy body composition and dose-limiting toxicities were not different for patients receiving adjuvant chemotherapy versus patients receiving neo-adjuvant chemotherapy (chapter 2). In addition, changes in body weight and body composition or baseline dietary intake did not differ between patients receiving adjuvant chemotherapy and patients receiving neo-adjuvant chemotherapy (chapter 4). In addition, changes in body weight and body composition did not differ between patients with a first measurement before chemotherapy versus patients with a first measurement during the first cycle of chemotherapy (chapter 4). Thus, including both adjuvant and neo-adjuvant treated patients did not affect the outcome of our study.

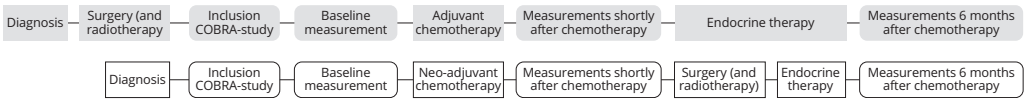


Figure 6.1. Schematic overview of moment of measurements for COBRA-study within treatment plan in patients treated with adjuvant chemotherapy (grey) and patients receiving neo-adjuvant chemotherapy (white).

One of the most important strengths of the COBRA-study compared to previous studies on changes in body weight and body composition is that we included a comparison group of women without cancer. This is important because all women change in body weight and body composition naturally over time, especially during menopause when they typically experience

an increase in body weight and fat mass and a decrease in lean muscle mass[30]. Because we included a comparison group, we were able to assess whether changes in body weight and body composition were different from natural changes over time (chapter 4). If we had chosen to only assess changes in fat mass in the patient group, we would have concluded that there is an increase in body fat over the study period. However, since we included a comparison group, we have been able to conclude that the increase in fat mass was not different from changes occurring naturally over time.

Information error and bias

Within the COBRA-study various instruments were used to collect data. Errors may be expected in our study measurements. When these errors were different between subgroups of our population with regard to the exposure and/or outcome this may have resulted in information bias.

Within this paragraph, some considerations regarding the information error and bias of three important measurements within the COBRA-study will be discussed, including the measurements of body composition, missing information regarding medication use, and dietary intake.

Body weight and composition

An important difference among studies is the method of data collection on body weight and body composition. Almost half of the included papers in our meta-analysis assessed body weight retrospectively by chart review[2,3,6,10,18,19,22,24,25,31], while most studies which prospectively assessed body weight used a scale to assess body weight[1,5,7,9,12-17,20]. Our meta-analysis showed that participants' body weight gain was less in studies which prospectively assessed body weight compared to studies which retrospectively assessed body weight (chapter 2).

In contrast to our study, most previous studies which prospectively assessed body weight changes in breast cancer patients used a scale[1,4,7,9,12-17,32]. It was not feasible to measure body weight with a scale on each moment of measurement in our study. Therefore, we used body weight assessed using Dual-Energy X-ray Absorptiometry (DEXA)-scan in this study. In a subgroup of 60 participants including patients and women of the comparison group, we measured body

weight on a scale as well as with the DEXA-scan on all three time points. Data from this subgroup showed that absolute body weight assessed by DEXA-scan is slightly lower than body weight measured by a scale. However, in chapter 4 we showed that changes in body weight over time were similar and not significantly different as measured by DEXA scan or scale. This suggests that using a DEXA-scan to assess body weight did not influence our results.

Methods employed to assess body composition also varied among studies, including DEXA[8,9,15-17,23,32,33], bio electric impedance (BIA)[4,11-13,15,26,27], and skinfold thickness[5,7], which all have their advantages and disadvantages. DEXA is a very accurate and valid method to assess body composition[34,35]. It is shown that DEXA-scans are a sensitive tool to assess small changes in body composition over time[36]. At present, there are two main DEXA manufacturers, Lunar and Hologic, whose scanners are used in clinical practice. It is shown that different types of scanners produce different results on body composition[37,38]. In the COBRA-study, types of scanners differed between the hospitals, therefore participants were measured three times in the same hospital with the same scanner.

A disadvantage of the use of DEXA-scan for measuring body composition during chemotherapy is the influence of body hydration on lean body mass results of the DEXA-scan[39,40], as hydration status of the body may change during chemotherapy. However, an assumption of using BIA to estimate body composition is a fixed hydration status of the body; therefore in earlier studies using BIA[4,11-13,15,26,27], changes in hydration status may also have caused inaccurate measures of body composition by BIA[41].

Because hydration status can affect lean body mass results of the DEXA scan, the increase in lean body mass in the patient group that was observed during chemotherapy in our study could be due to an increase in body fluid, especially since it returned back to baseline values 6 months after chemotherapy. One possible explanation for the increase in body fluid during chemotherapy could be the use of a more recent chemotherapy regime for breast cancer including docetaxel, which can cause fluid retention[42]. Besides docetaxel, dexamethasone, which is frequently prescribed during chemotherapy, can cause fluid retention as a side effect.

Missing information regarding medication use

Information regarding use of medication is difficult to collect. Most studies did not include medication use or they collected data via medical records. In our study, information regarding use of medication was gathered via calendar log sheets. Each participant was asked to complete a calendar log sheet, on which information regarding type of drug, dose and amount was collected for the total study period. These data are important because anti-emetic drugs used in breast cancer treatment can influence body composition. Dexamethasone, for example, may cause fluid retention. Unfortunately, because many different drugs were used, it proved to be very difficult to get a complete overview of used medication used during chemotherapy, even with the log sheets. As a consequence, it was not possible to take medication use during chemotherapy into account in our analyses and to assess whether changes in lean body mass differed by medication use which is similar in other studies.

Dietary intake

In general, self-reported dietary assessment methods may be influenced by several errors including socially desirable answers, and the difficulty to recall past dietary intake and to correctly estimate portion sizes.

Both the methods used and the time points when dietary intake was assessed are heterogeneous in previous studies. Methods commonly used to assess dietary intake in breast cancer patients are food records [8,11,12,14,32,33], food frequency questionnaires[5,9] and 24-hr dietary recalls[1,9]. Most previous studies assessed dietary intake during chemotherapy in the week before the next chemotherapy infusion, while we assessed actual dietary intake on random days during the full cycle of chemotherapy using a 24-hr dietary recall. Since we assessed actual dietary intake during the full cycle of chemotherapy, we captured the full variation in dietary intake over the course of chemotherapy. Energy intake varied among the weeks of chemotherapy cycle in our study (chapter 5); with the lowest intake in the first week and the highest intake in the week prior to the next cycle, although this did not reach statistical significance.

We estimated habitual dietary intake with a FFQ. We used 24-hr dietary recalls to assess actual dietary intake because we expected a large day-to-day variation during chemotherapy in the

patient group. Because we included only two 24-hr dietary recalls per participant we could not precisely assess dietary intake on an individual level, however two 24-hr dietary recalls per participant can provide an accurate estimate of the mean for a group, although the standard deviation will be overestimated[43].

As a consequence of using a combination of FFQ and 24-hr dietary recall to assess dietary intake within the COBRA-study, it was not possible to assess changes in dietary intake of patients between the start and end of chemotherapy. However, it was possible to assess differences in dietary intake between the patient and comparison group (chapter 5) and to assess whether usual dietary intake before start of chemotherapy was associated with changes in body composition over time (chapter 4).

Differences in BMI between the patient and comparison group could induce differential misreporting, since persons with a higher BMI tend to underestimate dietary intake more than persons with a lower BMI. In the sample of participants included in chapter 5, BMI was 1.4 kg/m^2 higher than in the patient group. This could have resulted in more underreporting of dietary intake in the patient group, therefore differences between the patient and comparison group could be overestimated.

Confounding

Confounding variables are variables that are associated with outcome and exposure, but are not an intermediate. Most previous studies on changes in body weight or body composition in breast cancer patients did not adjust for any confounding factor[1-8,10-13,15,16,18,20,22-24,26,31-33]. In order to minimize confounding in the COBRA-study, we attempt to include a patient group and comparison group which were as similar as possible. To ensure that the two groups were as similar as possible with regard to social economic status, education level, and lifestyle factors, we recruited the participants in the comparison group via the patient's network. In addition, both groups were matched on age to be able to assess changes naturally over time. Despite this method of recruitment, there were more highly educated women in the comparison group than in the patient group. Furthermore, women in the comparison group had a lower

BMI compared to patients. Therefore, women in the comparison group could be more health conscious. Because of the differences in education level and BMI, analyses of differences in dietary intake during chemotherapy between patients and comparison group were adjusted for different factors including education level and BMI in chapter 5. In chapter 4, changes in body composition between the two groups were adjusted for different factors including education level. Because BMI is highly correlated with body composition, we did not include BMI in these analyses. Including BMI in our analyses could therefore have led to overadjustment.

Despite adjusting for various potential confounders, residual confounding can never be completely ruled out, because of unmeasured or inaccurately measured potential confounding factors.

Selection error and bias

Selection bias can occur at different stages of a study; at the stage of recruitment of participants and/or during the process of retaining them in the study. Possible selection bias in these two phases of the study will be discussed in this paragraph.

Women in the patient group were included by the medical staff of participating hospitals. Recruitment via medical staff of hospitals could be a source of selection bias, since the staff decides which patient to invite. It is possible that patients who were more ill or more emotional at diagnosis did not get an invitation to participate in the study. Therefore, it is possible that the selection of breast cancer patients for our study is biased.

Another potential source of selection bias may be the competitive studies conducted in breast cancer patients in hospitals in the Netherlands. In some hospitals various studies in breast cancer patients are conducted simultaneously. Therefore, some hospitals decided in advance which patients were asked for which study and which participants for another study depending on inclusion criteria. Therefore, it is also possible that a specific group of patients in a hospital was asked to participate in our study e.g. more patients receiving a particular type of chemotherapy or having a particular hormone receptor status. However, by recruiting in 11 hospitals, we expect this type of selection bias was limited in our study.

Participants in the comparison group were recruited via the patient group. Some patients were able to recruit several women, while others could not include anyone. Therefore, it is possible that the comparison group consists of specific women who are less comparable to the patient group. Nevertheless, women of both groups were quite similar, except in terms of education level and BMI.

Next to potential selection, also differential los to follow-up may lead to selection error. In the COBRA-study approximately 10% of the patients dropped out during the study period compared to 7% in the comparison group. Women in the patient group dropped out most often during or shortly after chemotherapy, due to illness during chemotherapy, or because the study burden was too high, while women in the comparison group dropped out because of a lack of time. When more women with more complaints during chemotherapy dropped out, this could have led to a group of patients with less complaints during chemotherapy. However, drop-out rates between the patient group and comparison group are quite similar within the COBRA-study.

Concluding information error and bias, confounding and selection error and bias may have slightly affected the internal validity of the COBRA-study. Nevertheless, the internal validity of the study appears to be high.

External validity

If the internal validity is considered to be high as discussed in the previous section, the next step is to assess the external validity. External validity refers to whether results of our study can be generalized to the total population of breast cancer patients.

In the patient population of our study 14% of the patients was diagnosed with a triple negative cancer, which is comparable with the results in the Dutch population where 15-20% is diagnosed with a triple negative tumour[44].

More than 50% of our participants in the patient and comparison group are classified as highly educated, whereas in the general Dutch population of women this was only 28% in 2012[45]. This could be explained by the fact that high educated persons seem to be more willing than

lower educated persons to participate in studies[46]. We may expect that the participants in our observational study are more health-conscious than the general Dutch population, and therefore have a healthier diet and lifestyle compared to individuals not participating in this study. In addition, because of the recruitment procedure in the hospitals, it is possible that patients are more fit in relation to the total population of women diagnosed with breast cancer. As a result of this, our results might not be generalizable to all women diagnosed with breast cancer and the female Dutch population.

Changes in breast cancer care

Breast cancer care has changed over time. In this paragraph, we discuss two important changes in breast cancer care that have to take into account when comparing our results with previous studies; the first is the change in chemotherapy over time and the second is the awareness among clinicians.

The types of chemotherapy that are used in clinical practice has change over time. In our prospective study we found a mean weight gain of 1.1 kg during chemotherapy, which is similar to the 1.4 kg body weight gain we found in our meta-analysis, including only women treated with newer chemotherapy regimes. In addition, three recent studies, not included in the meta-analysis showed no change, or only a slightly gain of 0.9 kg in eight during chemotherapy for early stage breast cancer[26,27,29]. Taken together, our meta-analysis, our prospective study and recent literature results suggest that weight gain during chemotherapy likely was greater in older studies as a result of changes in chemotherapy treatment.

Another possible explanation for less weight gain in more recent studies could be the clinicians' awareness of possible changes in body weight and body composition during chemotherapy which may in turn lead them to better inform patients about possible changes during chemotherapy. Currently, many patients receive an invitation for an exercise program during and/or after chemotherapy e.g. *fit en balans* and *herstel en balans*. Because of participating in such a program it is possible that women are more active during the treatment and more aware of changes in body weight than those who are not participating in such program.

Conclusion

In conclusion, this thesis suggests that pre-treatment fat mass is associated with dose-limiting toxicities during chemotherapy. Weight gain during chemotherapy appeared to be more modest than we expected based on literature, and changes in body composition during chemotherapy consist mainly of an increase in lean body mass, which is only temporary and returned to baseline within 6 months after chemotherapy. A higher appetite during chemotherapy was associated with changes in body weight and body composition. A younger age at diagnosis was associated with greater changes in body weight and fat mass, but not with changes in lean body mass. In addition, an ER-receptor negative tumour was associated with greater changes in body weight, but not with changes in fat mass or lean body mass. During chemotherapy, women with breast cancer have a lower intake of energy, fat, protein and alcohol compared to age-matched women without cancer, which was expressed by a lower intake of specific food groups. The results of this thesis do not suggest that dietary intake is associated with weight gain during chemotherapy.

Implications for clinical practice and future research

Despite the fact that this thesis suggests that weight gain is only modest currently, and the changes are temporary during chemotherapy but normalize in the 6 months after chemotherapy, it is still important for clinicians to inform patients about the potential changes in body weight and body composition. This is especially important for younger women. In addition, given the wide range in changes in body weight and body composition observed there are certain patients who will gain a lot of weight and change in body composition. Thus it remains important to monitor changes over time, especially since previous studies putatively suggested that changes in body weight and body composition may be associated with recurrence and mortality[47-49].

A longer follow-up of the COBRA-study is recommended because of the following two reasons. First, in de patient group we found a trend toward an increase in fat mass during the 6 months after chemotherapy. A longer follow-up is desirable, to investigate whether fat mass in the patient group further increases and changes different from the fat mass in the comparison in the period after chemotherapy.

The second reason is our inclusion of adjuvant and neo-adjuvant treated patients in our study. At the moment of the last measurements the patients in the neo-adjuvant group had just started their endocrine treatment, while the adjuvant group was receiving endocrine treatment usually already for several months. When following patients for a longer time, the effect of hormone treatment could be investigated within the COBRA-study.

Within this thesis we utilized only a portion of the data collected within the COBRA-study. Therefore, before starting a new study regarding changes in body weight and body composition in breast cancer further analyses within the COBRA-study can be conducted. For example, in addition to data on body weight, data on chemosensory changes were collected within the COBRA-study. A recent study suggests that patients who experience no, or mild chemosensory changes are the patients whose body weight remains stable, or who gain weight [50], but results are inconsistent [51]. This could be further investigated within the COBRA-study, including other factors that may influence changes in body weight and body composition. At the moment of submission of this thesis, data collection for the COBRA-study was still ongoing. Therefore, not all data of all patients and women of the comparison group were included in the analyses of chapter 4. In due time, the analyses of chapter 4 will be repeated with the total study group, those analyses will have more statistical power to assess possible determinants of changes in body weight and body composition.

The results on pre-treatment body composition and dose-limiting toxicities of this thesis may not have direct implication for the clinical practice because consequences of administering chemotherapy based on body composition instead of body surface area are unknown. Furthermore, we were the first to assess the association of fat mass and dose- limiting toxicities during chemotherapy in breast cancer patients. Therefore, more research is needed to assess whether fat mass is indeed associated with dose-limiting toxicities and what consequences this may have on recurrence and disease-specific survival.

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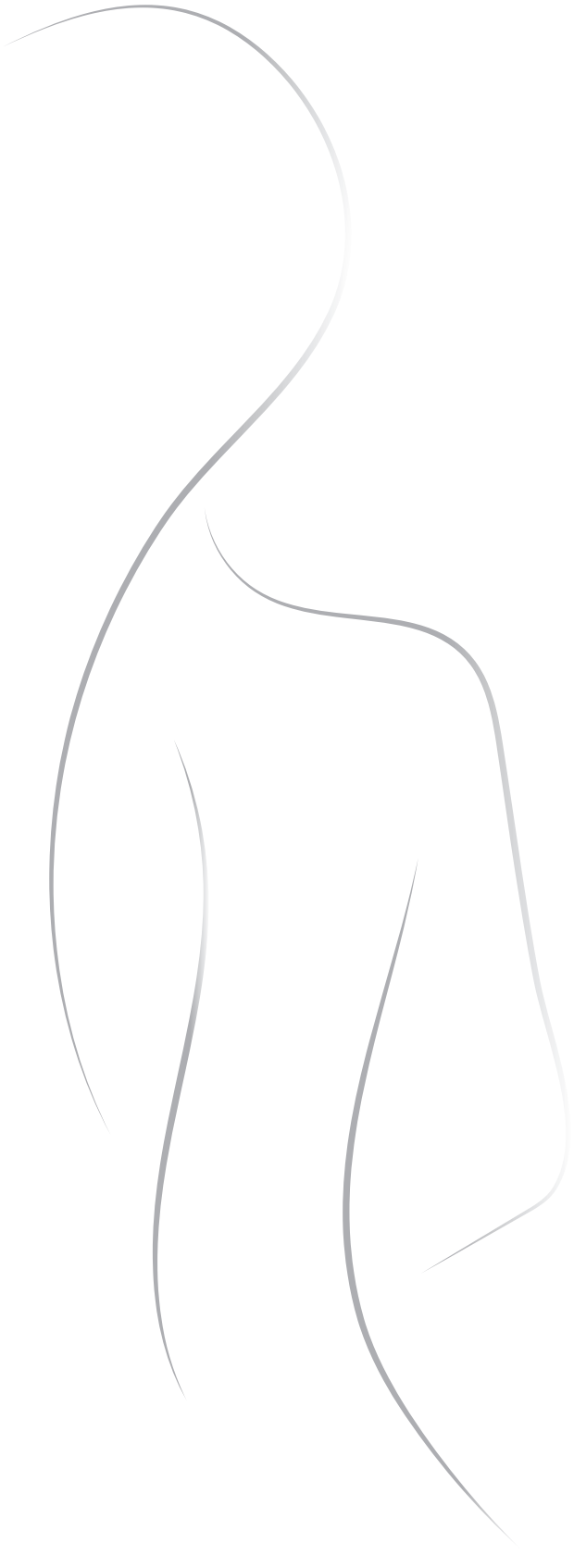


Summary

Summary

Because of the improved survival rate, both short term and long term adverse effects of breast cancer treatment have become increasingly important. Body weight and body composition before, during, and after chemotherapy may influence side effects during treatment and survival. The aims of this thesis were to assess among stage I-IIIB breast cancer patients: 1) the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy, 2) potential changes in body weight and body composition during and after chemotherapy compared to changes in age-matched women without cancer in the same time period, and 3) dietary intake during chemotherapy compared to age-matched women without cancer in the same time period.

Chapter 2 describes the association between pre-treatment body composition and dose-limiting toxicities during chemotherapy. Data from 172 breast cancer patients who participated in the COBRA-study were analysed. Body composition was measured using a total body Dual Energy X-ray Absorptiometry (DEXA) scan. Information regarding dose-limiting toxicities was abstracted from medical records. A higher BMI (kg/m^2) and a higher fat mass (kg and percentage) were associated with an increased risk of dose-limiting toxicity, while lean body mass (kg) was not associated with risk of toxicities.

Chapter 3 presents the findings of a meta-analysis on changes in body weight during chemotherapy in breast cancer patients. The meta-analysis showed an overall gain in body weight of 2.7 kg (95% CI: 2.0-3.3) during chemotherapy, with a high degree of heterogeneity (I^2= 94.2%). Weight gain in breast cancer patients was more pronounced in papers published before 2000 and studies including cyclophosphamide, methotrexate and 5-fluorouracil as chemotherapy regime.

Chapter 4 describes changes in body weight and body composition during and after chemotherapy. Data from 145 patients and 121 women of an age-matched comparison group, participating in the COBRA-study were analysed. Body composition was measured using DEXA-scan at three time points during the study period. For the patient group, these time points were:

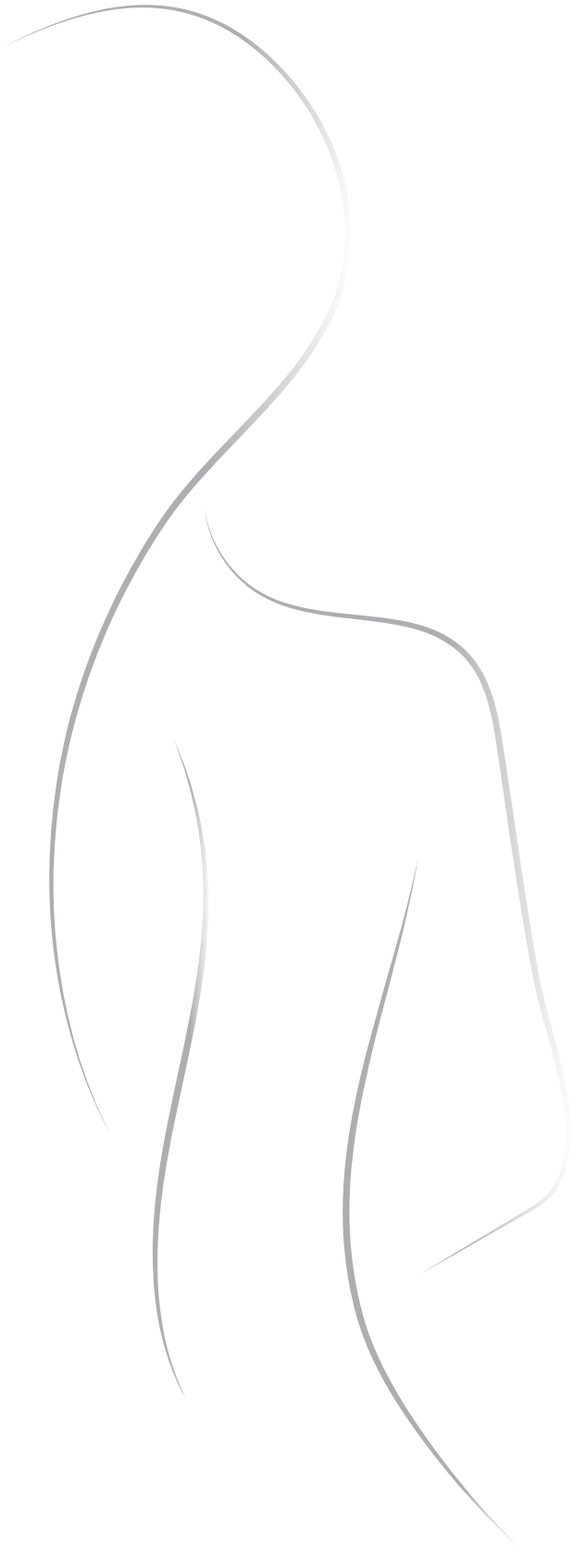
before start of chemotherapy, shortly after chemotherapy, and 6 months after chemotherapy. For the comparison group these measurements were conducted over a similar time frame: baseline, 6 months after baseline, and 12 months after baseline. In addition, we identified determinants of changes in body weight and body composition.

Shortly after chemotherapy, patients had a significantly higher body weight, BMI, and lean body mass than women in the comparison group, while fat mass was similar. Six months after chemotherapy no differences in body weight or body composition were observed between the patient and comparison group. A younger age, better appetite during chemotherapy, and an ER-receptor negative tumour were associated with greater changes in body weight over time. A younger age and better appetite during chemotherapy were associated with greater changes in fat mass over time, while the only determinant associated with greater changes in lean body mass over time was a better appetite during chemotherapy.

Chapter 5 describes the dietary intake and food groups before and during chemotherapy of breast cancer patients compared with women without cancer. In addition we assessed the association between symptoms and energy intake. Data from 117 breast cancer patients and 88 women without breast cancer who participated in the COBRA-study were used. Habitual dietary intake before chemotherapy was assessed using a food frequency questionnaire. Two 24-hr dietary recalls were used to assess actual dietary intake during chemotherapy for patients and within 6 months for the comparison group. Shortly after the 24-hr dietary recall, participants filled out questionnaires about symptoms. Before chemotherapy, dietary intake was similar for both groups. During chemotherapy, breast cancer patients reported significantly lower total energy, total fat, total protein, and alcohol intake than women without cancer, which could be explained by a lower intake of specific food groups.

Overall results from this thesis suggest that pre-treatment fat mass is associated with dose-limiting toxicities during chemotherapy. Weight gain during chemotherapy appeared to be more modest than we expected based on literature and changes in body composition during chemotherapy consist mainly of an increase in lean body mass, which is only temporary

and returned to baseline within 6 months after chemotherapy. A higher appetite during chemotherapy was associated with changes in body weight and body composition. A younger age at diagnosis was associated with greater changes in body weight and fat mass, but not with changes in lean body mass. In addition, an ER-receptor negative tumour was associated with greater changes in body weight, but not with changes in fat mass or lean body mass. During chemotherapy women with breast cancer have a lower intake of energy, fat, protein and alcohol compared to age-matched women without cancer, which was expressed in a lower intake of specific food groups. The results of this thesis do not suggest that dietary intake is associated with weight gain during chemotherapy.



Dankwoord

Dankwoord

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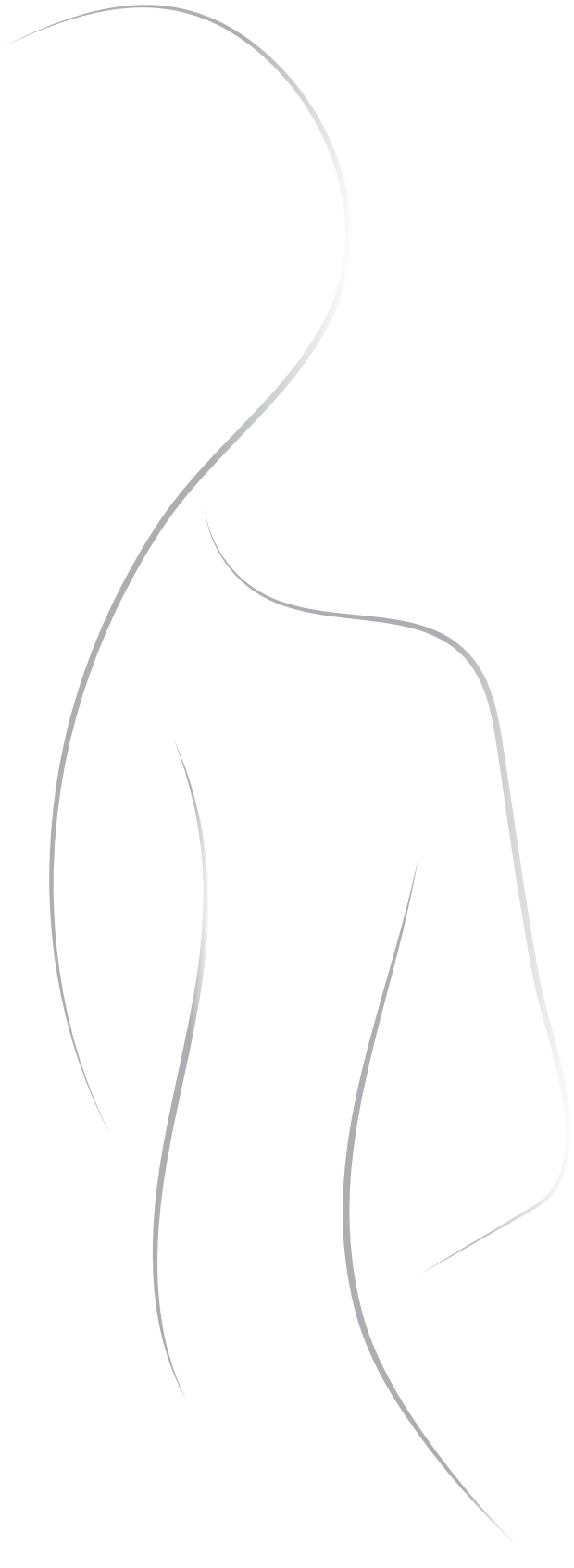
Maaike



About the author

Curriculum vitae

Maaike Maria Gijsberdina Adriana van den Berg was born on March 8th, 1985 in Veghel, the Netherlands. After completing seccondary school at Udens College in Uden in 2003, she started studying Medical Imaging and Radiation Therapy (MBRT) at Fontys Universiy of Applied Sciences in Eindhoven. For her first clinical internship she worked at the department of Radiology at Bernhoven hospital in Oss. Maaike completed her second clinical internship at the department Nuclear Medicine of the Radboudumc, Nijmegen. For her research thesis she went to the department of Nuclear Medicine at the St. Antonius hospital in Nieuwegein, were she studied the Quantification of 18F-FDG-uptake in the lung parenchyma by sarcoidosis patients. After graduating, Maaike worked as a Medical Nuclear Worker at the department of Nuclear Medicine at Radboudumc, Nijmegen. In 2008, Maaike started the premaster Biomedical Sciences at Radboud University in Nijmegen after which she started the MSc program in 2009, specializing in the field of Epidemiology. For her MSc thesis she went to the department Psychosocial Research and Epidemiology at the Netherlands Cancer Institute, Amsterdam, where she studied the effects of mediastinal radiation and anthracycline containing chemotherapy on the risk of myocardial infarction following treatment for Hodgkin Lymphoma. In 2011, she completed her Master with the specialization Epidemiology. In April 2012, Maaike started her PhD program at Wageningen University. She executed her PhD research under the supervision and guidance of Prof. Ellen Kampman, Prof. Marjolein Visser, Dr Renate Winkels and Dr Jeanne de Vries. This project was funded by the Dutch Cancer Society. Her research focussed on changes in body composition during chemotherapy in breast cancer patients. During her PhD, Maaike joined the educational program of the graduate school VLAG. She attended several (inter)national conferences and courses and was involved in teaching and supervising BSc and MSc students during their thesis Projects. Currently Maaike works as a research coordinator at the Catharina Hospital in Eindhoven.

List of publications

Publications in peer-reviewed journals

Berg, M.M.G.A. van den; Winkels, R.M.; Kruif, J.Th.C.M. de; Laarhoven, H.W.M. van; Visser, M.; Vries, J.H.M. de; Vries, Y.C. de; Kampman, E. (2017). Weight change during chemotherapy in breast cancer patients: A meta-analysis. BMC Cancer 17(1). Doi:10.1186/s12885-017-3242-4

Vries, Y.C. de*; **Berg, M.M.G.A. van den***; Vries., J.H.M. de; Boesveldt, S. ; Kruif, J.Th.C.M. de; Buist, N. ; Haringhuizen, A. ; Los, M. ; Sommeijer, D.W. ; Timmer-Bonte, J.H.N. ; Laarhoven, H.W.M. van; Visser, M. ; Kampman, E. ; Winkels, R.M. (2017) Differences in dietary intake during chemotherapy in breast cancer patients compared to women without cancer. Supportive Care in Cancer 25 (8). - p. 2581 - 2591. *shared first authorship

Vries, Y.C. de; Winkels, R.M.; **Berg, M.M.G.A. van den**; Graaf, C. de; Kelfkens C.S: Göker E.; Grosfeld S.; Sommemeijer D.W.; Laarhoven, H.W.M. van; Kampman, E.; Boesveldt, S. (2017). Altered food preferences and chemosensory perception during chemotherapy in breast cancer patients: A longitudinal comparison with healthy controls. Food quality and preference, 63, 135-143. doi: 10.1016/j.foodqual.2017.09.003

Submitted publications

Berg, M.M.G.A. van den;. Kok D.E.G; Posthuma, E.E.; Kamps, L.; Kelfkens, C.S.; Buist, N.; Geenen, M.; Haringhuizen, A; Heijns, J.B.; Lieshout, R.H.M.A. van; Los, M.; Sommemeijer, D.W.; Timmer-Bonte, J.N.H;. Kruif, J.Th.C.M. de; Laarhoven, H.W.M. van; Kampman, E.; Winkels, R.M. Body composition is associated with risk of dose-limiting toxicities during chemotherapy in women with stage I-IIIB breast cancer.

Vries, Y.C. de; Kelfkens, C.S.; Posthuma, E.E.; Boesveldt, S.; **Berg, M.M.G.A. van den**; Kruif, J.Th.C.M. de; Haringhuizen, A; Sommemeijer, D.W.; Buist, N; Grosfeld, S; Graaf, C. de; Laarhoven, H.W.M. van; Kampman, E.; Winkels, R.M. Chemosensory determinants of quality of life after systemic therapy for breast cancer: The importance of trastuzumab.

Overview of completed training activities

	Organiser and location	*Year*
Discipline specific courses and activities		
Courses		
Exposure Assessment in Nutrition Research	VLAG, Wageningen	2012
Course 'Basic Oncology'	NVVO, Ellecom	2013
Course 'Qualitative research in the practice of health care'	Epidm, Amsterdam	2013
Masterclass Longitudinal data analysis'	VLAG, Wageningen	2013
Masterclass 'Confounding'	VLAG, Wageningen	2014
Masterclass 'Diet and Cancer'	VLAG, Wageningen	2014
Masterclass 'Mixed Models'	VLAG, Wageningen	2017
Concepts and Methods in Epidemiology	WUR, Wageningen	2012-2013
Conferences and meetings		
Evening symposium oncology days	V&VN, Ede	2013
Symposium 'Oncologie dicht bij de patient'	ZGV, Ede	2014
Annual meeting of the Netherlands Epidemiology Society	VvE, Leiden	2014
International symposium on Body Composition	ISBCR. Cascais, Portugal	2014
A-care symposium	A-care, Amsterdam	2014
Oncology Days	V&VN, Ede	2014
European breast cancer conference	European cancer organisation, Amsterdam	2016
General courses and activities		
VLAG PhD week	VLAG, Baarlo	2012
Mini-symposium 'How to write a world class paper'	VLAG, Wageningen	2013
Interpersonal communication	WGS, Wageningen	2014
Philosophy and Ethics of Food Science and Technology	WGS, Wageningen	2015
Scientific writing	Wageningen in'to Languages, Wageningen	2015
Teaching and supervising thesis students	ESD, Wageningen	2015
Optional courses and activities		
Preparation of research protocol	WUR, Wageningen	2012
PhD study tour Division of Human Nutrition	WUR, East coast USA	2015
Food for Thought	Alliantie voeding, Ede	2012-2017
Staff seminars & chair group meetings	WUR, Wageningen	2012-2017

Colophon

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