Weight Change of Younger and Older Early Breast Cancer Patients – A Meta Regression

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Abstract

**Introduction:** Weight gain has a major impact on the quality of life of breast cancer patients. Post-treatment weight gain can impact on primary endpoints such as recurrence, death, self-identity and the ability to return to work. Parameters thought to impact on weight gain include menopausal status, age and chemotherapy regimen. Using meta-regression, we studied the effect of age on weight change, by menopausal status and chemotherapy regimen.

**Methods:** 24 studies were identified, and extracted for weight change, mean/median age, menopausal status and chemotherapy regimen. A meta-regression was performed, using a random-effects DerSimonian and Laird model for high heterogeneity and fixed-effects inverse-variance model for low heterogeneity. Subgroup analyses were conducted, by menopausal status and chemotherapy regimen. P-values less than 0.05 were considered statistically significant.

**Results:** There exists no relationship between weight change and age ($\beta = 0.00; p = 0.987$). Stratifying by menopausal status and chemotherapy regimens, there likewise was no relationship.

**Conclusion:** Management of weight gain due to chemotherapy has been focused on relatively young women where a higher mortality and recurrence has been found. However, our results suggest that age should not be used to differentiate care in these patients.

Introduction

For patients receiving chemotherapy for early-stage breast cancer, weight gain has been frequently reported\(^1,2\). This weight gain can negatively impact quality of life and self-esteem. Mechanisms include increased edema, with decreased physical activity leading to fatigue. Important changes in body composition (BMI) is especially pronounced in younger women, who become postmenopausal due to chemotherapy. Despite less weight gain with more recent chemotherapy regimens, this change in BMI continues to impact breast cancer prognosis and development of other medical conditions, such as heart disease, which is a significant cause of mortality in breast cancer survivors\(^3\)–\(^6\); Thivat *et al*\(^7\) report that a 5% or greater weight change is associated with increased risk of recurrence (RR: 2.28, 95% CI: 1.29–4.03) and death (RR: 2.11, 95% CI: 1.21–3.66).

Prevalence of weight gain has been reported to between 50–96%, and weight gain can vary from, on average, 1.4kg to 6.2kg\(^8\). van den Berg *et al*\(^9\), in a systematic review and meta-analysis, found that body weight increased by 2.7kg during chemotherapy. Their sensitivity analyses by study design, menopausal status, chemotherapy regimen and year of publication showed variation in weight gain. However, their review cited high heterogeneity, suggesting that there may be a confounder in their analysis.

Age has previously been reported to affect weight gain, in a large population-based cohort study of 4,561 patients. Chen *et al* reported that younger breast cancer patients experienced greater weight change\(^9\). Based on their results, one may infer that studies with younger patients will observe a greater weight
change. The observed variations reported by van den Berg et al, by chemotherapy regimen and menopausal status, may therefore be a confounded observation, by age. Clarifying this issue is important, as it will inform whether age of patients should be considered, when enacting interventions for weight change. Additionally, it will clarify whether menopausal status and chemotherapy regimen still has an effect on weight change, after accounting for the potential confounder of age. A meta-regression can be used in this setting, to investigate the effect of age in the causal pathway and provide clarification on whether age may have been a contributing factor to high heterogeneity in the van den Berg et al meta-analysis.

To investigate whether age has an effect on weight change, we conducted a meta-regression for studies reporting on chemotherapy use in early-stage breast cancer patients.

**Methods**

We searched the databases of Ovid Medline, Embase and Cochrane Central Register of Controlled Trials for studies reporting on weight change in early breast cancer patients, using the MeSH headings of “breast neoplasms”, “neoplasm staging” and “body-weight trajectory”. We identified the same 25 studies for inclusion as those reported by van den Berg et al in their systematic review were included in this analysis. We could not find the full-text for the article written by Foltz, which was one of the 25 papers included by van den Berg et al. Therefore, 24 papers were included in this analysis as pertinent details from the full text article are required for meta-regression. The effect size of weight gain for each study was extracted and cross-referenced with those reported by van den Berg et al. The age of patients included in the study, as reported using measures of central tendency (mean or median), was noted. Additionally, the menopausal status of patients enrolled in studies were recorded, either as reporting exclusively on (1) premenopausal patients, (2) postmenopausal patients, and (3) premenopausal and postmenopausal patients. Finally, we recorded whether patients received (1) CMF chemotherapy only, (2) CMF chemotherapy, alongside other, or (2) other chemotherapy treatment, and not CMF chemotherapy.

A random-effects DerSimonian and Laird model was used when heterogeneity was high ($I^2 > 50\%$) and fixed-effect inverse-variance model ($I^2 < 50\%$) was used, to meta-regress effect size relative to age of patients. Subgroup analyses were conducted, by menopausal status of patients and by chemotherapy treatment. The threshold for statistical significance was specified, a priori, at $\alpha = 0.05$. All analyses were conducted using Stata 16.1.

**Results**

The average age in trials ranged from 39.9 years to 55 years. Six studies reported on premenopausal patients, four on postmenopausal patients, and fourteen reported on both premenopausal and postmenopausal patients. Seven, nine, and seven patients received CMF chemotherapy only, CMF chemotherapy, alongside other, and other chemotherapy treatment, respectively.
and twelve studies\textsuperscript{12–15, 18, 20, 22, 25–28, 33} reported on CMF-only, CMF-containing and non-CMF regimens, respectively; several studies reported separately, by chemotherapy regimen.

Across all studies, there exists no relationship between weight change and age – $\beta = 0.00$ and $p = 0.987$ (Fig. 1). In subgroup analyses of premenopausal and postmenopausal patients, there also exists no relationship – $\beta = 0.05$ and $p = 0.150$ for premenopausal patients, and $\beta = 0.09$ and $p = 0.588$ for postmenopausal patients (Fig. 2). When analyzing separately by chemotherapy regimen, there likewise was no relationship between weight gain and age (Fig. 3).

Discussion

To our knowledge, this is the first meta-regression reporting on weight change as a function of age. We report on 24 studies, with a total sample size of 2,586 patients. There is no relationship between age and weight change among early-stage breast cancer patients undergoing chemotherapy, which prevails in all subgroup analyses. Age is not a confounder in the relationships between chemotherapy regimen and weight change, and menopausal status and weight change.

This study was able to address the myth that weight gain is a larger problem for younger women, due to chemotherapy-induced menopause. This study reports otherwise, that both younger and older women experience similar degrees of weight change.

This study also provides further guidance on clinical decision making. Patients often ask about weight gain and the answer may influence their selection of chemotherapy regimen or even willingness to accept treatment. Physicians query weight gain as well as it has a significant impact on recurrence rates and quality of life. This study provides a means to inform patients with accurate data and to guide physicians in focussing not on age, but rather on other weight gain predictors. Since age is not an independent risk factor for weight gain, decisions on which patients require more intensive intervention for preventing weight gain should be based on evidence from studies exploring body composition, metabolism and insulin resistance instead.\textsuperscript{4} Given studies demonstrating higher morbidity and mortality among breast cancer patients with higher BMI, patients of all ages, not just younger patients, should be encouraged to maintain a healthy weight following their breast cancer diagnoses. Furthermore, as noted in the prior review by van den Berg \textit{et al}\textsuperscript{8}, different magnitudes of weight gain were noted by menopausal status and chemotherapy regimen\textsuperscript{8}; these factors should be heavily considered irrespective of age, when considering intervention options.

A limitation of this study, like other evidence synthesis studies, is that its validity is reliant on the validity of included studies. As reported by van den Berg \textit{et al}\textsuperscript{8}, some included studies were not of the highest quality, as assessed using the Newcastle-Ottawa scale. As well, one may have concerns about reporting bias, where only certain age groups are reported in the literature. However, included studies had a wide range of average ages, spanning 15 years.
In conclusion, there is no relationship confounding effect of age on weight change in early-stage breast cancer patients. This was observed, among both premenopausal and postmenopausal patients, as well as patients receiving CMF chemotherapy and other chemotherapy regimens.

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**References**


Figures
Figure 1

Weight Change, as a Function of Age, in All Early Breast Cancer Patients ($\beta = 0.00; p = 0.987$) Note: Each circle indicates an individual study’s results. The size of the circle denotes the weighting, in the meta-regression model.
Figure 2

Weight Change, as a Function of Age, for 2.1 Premenopausal Patients ($\beta = 0.05; p = 0.150$) 2.2 Postmenopausal Patients ($\beta = 0.09; p = 0.588$) 2.3 Premenopausal and Postmenopausal Patients ($\beta = -0.14; p = 0.546$)
Figure 3

Weight Change, as a Function of Age, for 3.1 Patients Receiving CMF Alone (β = -0.07; p = 0.562) 3.2 Patients Receiving CMF, In Addition to Others (β = 0.08 p = 0.707) 3.3 Patients Not Receiving CMF (β = 0.02; p = 0.807)