



## Original article

# Predictors of weight gain in a cohort of premenopausal early breast cancer patients receiving chemotherapy



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## ABSTRACT

**Aim:** In breast cancer patients, post chemotherapy weight gain is linked with increased risk of cancer recurrence. We prospectively studied a cohort of premenopausal women receiving contemporary chemotherapy following a diagnosis of breast cancer to examine factors predicting weight increase.

**Methods:** Between May 2005 and January 2008, 523 patients from the Prospective Outcomes in Sporadic versus Hereditary (POSH) breast cancer study entered this sub-study comparing weight prior to chemotherapy and weight and waist/hip measurements 12-months following chemotherapy.

**Results:** Data from 380 patients were available. Mean (standard deviation [SD]) pre-treatment body mass index (BMI) was 26.3 (5.6) kg/m<sup>2</sup>; 30% women gained > 5% body weight during the study period. Lower BMI at diagnosis predicted greater subsequent post treatment weight gain (4.3% relative weight gain for those in the 1st quartile of BMI compared to 0.8% for those in the 4th quartile;  $r = -0.22$ ;  $p < 0.001$ ). No link to chemotherapy regimens, cigarette smoking, previous parity or chemotherapy induced amenorrhoea was noted. A total of 44% of women had central obesity (post-treatment waist measurement of  $\geq 88$  cm).

**Conclusions:** Almost a third of premenopausal patients receiving adjuvant chemotherapy for breast cancer will gain clinically significant weight and over 40% will have central obesity 12-months following diagnosis. A greater weight gain is predicted by lower pretreatment BMI.

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## 1. Introduction

Weight gain above increases seen with normal aging is common following a diagnosis of early breast cancer [1,2]. Post diagnosis weight gains of 2.0–7.5 kg have been reported, mainly occurring in

the first year after diagnosis and during adjuvant treatments [3]. This assumes importance as it can negatively affect the prognosis of breast cancer survivors by increasing risks of loco-regional and late recurrence [4–6] although this is not a universal finding [7]. Furthermore, there are other associated undesirable effects of weight gain on quality of life, cardiovascular health and lymphoedema risk [8–10].

Post diagnosis weight gain in breast cancer survivors has complex aetiology and may be influenced by patient-related factors (e.g. age, menopausal status) or treatment related factors. More so

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than endocrine therapy, chemotherapy is associated with weight increase as up to 50% of women receiving chemotherapy may gain more than 5% of body weight in the first year after diagnosis [11].

Previous studies which have examined weight gain amongst women receiving adjuvant chemotherapy have included both pre- and post-menopausal women [6] or a range of chemotherapy regimens [12]. The latter is important as a recent meta-analysis suggests that more modern taxane and anthracycline regimens are associated with less weight gain than historic regimens such as cyclophosphamide, methotrexate and fluorouracil (CMF) [3].

We report findings of a prospective study exploring the prevalence of significant weight gain (>5% of pretreatment weight [4,11]) amongst premenopausal women receiving contemporary taxanes/anthracycline adjuvant chemotherapy for early breast cancer.

## 2. Methods

The multicentre Prospective Study of Outcomes in Sporadic versus Hereditary Breast Cancer (POSH study) recruited 2956 patients aged 40 years or younger from 127 hospitals in the UK. The primary aim was to determine the effect of a germline BRCA1 or BRCA2 mutation on breast cancer outcomes in patients with young-onset breast cancer [13]. Details of recruitment and design of the POSH study have been previously published [13]. Between May 2005 and January 2008, patients entering the POSH study were also invited to enter this weight gain sub-study. Recruited patients underwent all measurements on two occasions, i) following surgery but prior to commencement of chemotherapy and ii) at 12-months ( $\pm 3$  months) having completed a course of chemotherapy. At both assessments, weight (kg), height (cm), body mass index (BMI), hip and waist measurements were recorded by study researchers using standardised methods i.e. around the umbilicus and the widest point of the trochanters as described previously [14]. Patient data including family history of breast cancer (1st or 2nd degree relatives) ethnic group, use of oral contraceptives, previous smoking history, changes in use of contraceptives or smoking in the 12-month study period, development of amenorrhoea during chemotherapy, type of breast surgery, tumour histology and systemic adjuvant therapy were recorded.

Women receiving neoadjuvant chemotherapy were excluded from this study to avoid potential weight gains prior to surgery confounding subsequent measurements [15].

Ethical approval was granted by the South West Multicentre Research Ethics Committee (MREC/00/6/69). Written informed consent was obtained from all trial participants.

Descriptive statistics (means, medians, standard deviations, range and percentages as appropriate) are presented for all patient characteristics, treatment-related factors and weight changes for the whole cohort and the subgroup with 12-months follow-up.

Relationships with weight gain are assessed using Pearson or Spearman correlations for normally distributed variables or non-normal ordered categorical data respectively, and t-tests or one-factor ANOVA for nominal factors. Multivariable linear regression analysis was used to identify significant independent predictors of weight change.

Two-sided tests and the conventional 5% significance level were used throughout.

## 3. Results

The weight sub-study recruited from 66 of the 127 recruiting centres in the UK and included approximately 70% of the patients recruited to the main POSH study from these centres during this time frame. A total of 523 patients were enrolled from which 380 premenopausal patients receiving chemotherapy for early breast

cancer were identified for this analysis (Fig. 1). Of these, 257 patients (68%) had post diagnosis weight and waist and hip measurements performed at 12-months ( $\pm 3$  months) post diagnosis. The remaining patients had weight measurements within the study period (May 2005–Jan 2008) but not within 12-months ( $\pm 3$  months) post diagnosis. Results are presented for the whole cohort ( $n = 380$ ) and the 12 ( $\pm 3$ ) months cohort ( $n = 257$ ).

Demographics of the whole and 12-months ( $\pm 3$  months) cohorts are included in Table 1. Treatment related factors were similar between the two cohorts and are described in Table 2. Mean age (SD) at diagnosis was 35.8y (3.7y) for the whole cohort and 36.0y (3.4y) for the 12-month cohort and mean (SD) pre-chemotherapy BMI was 26.3 (5.6) and 26.0 (5.2) respectively. These findings are consistent with those of the POSH study [13] in which the 2956 study participants had a mean age of 35.5y (SD 3.7y) and mean BMI of 25.9 (SD 5.5).

Weight change and waist and hip measurements are reported in Table 3. Mean (SD) pretreatment weight was 71.3 kg (16.0 kg) and 70.4 kg (15.5 kg) within the whole cohort and the 12-month cohort respectively. Gains of 5% or more of body weight occurred in 30% of the whole cohort and 32% of the 12-month cohort. Lower pretreatment BMI was associated with higher percentage weight gain ( $r = -0.22$  and  $-0.23$  for the whole and 12-month cohorts respectively; both  $p < 0.001$ ; Pearson correlation). Mean relative weight gain in the whole cohort was 4.3% for those in the 1st quartile of BMI compared to 0.8% for those in the 4th quartile (Table 4). On multivariate analysis, only pretreatment BMI was predictive of subsequent weight gain (regression parameter  $-0.26$  and  $-0.29$  in overall and 12-month cohorts respectively;  $R^2 = 5\%$  and  $6\%$  respectively; both  $p < 0.001$ ).

In the 12-month cohort a statistically significant association was

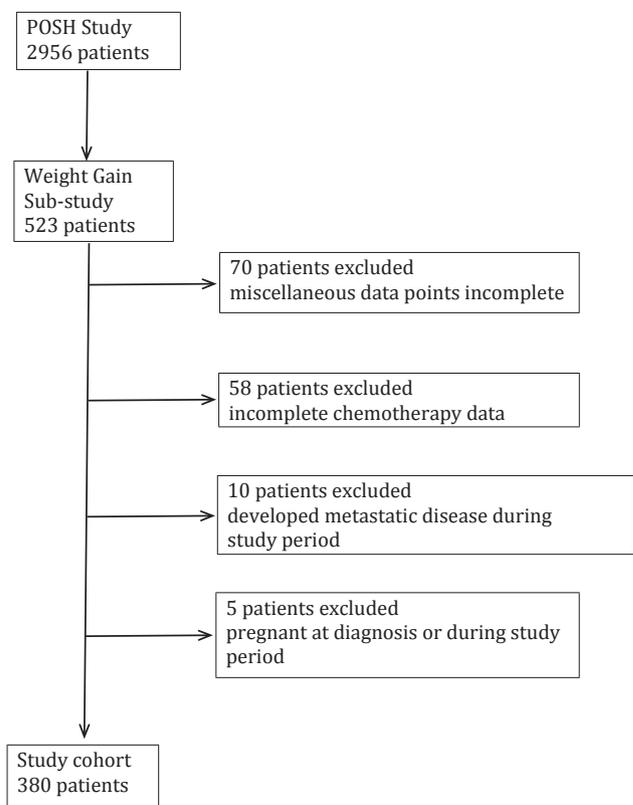


Fig. 1. Recruitment into Weight Gain Substudy from the Prospective study of Outcomes in Sprodic & Hereditary (POSH) study.

**Table 1**  
Characteristics of premenopausal breast cancer patients in the POSH weight gain sub study.

	Whole cohort (n = 380)	12 months cohort (n = 257)
Age at diagnosis (years)		
mean	35.8	36.0
(s.d.) range	(3.7) 20 - 40	(3.4) 24 - 40
BMI <sup>a</sup> at diagnosis (kg/m <sup>2</sup> )		
mean (s.d.)	26.3	26.0
range	(5.6) 17.8–51.1	(5.2) 17.8–44.6
Ethnicity		
White	352 (93%)	237 (92%)
Asian	12 (3%)	8 (3%)
Black	14 (4%)	10 (4%)
Other	2 (1%)	2 (1%)
Number of children		
0	103 (27%)	66 (26%)
1	80 (21%)	32 (20%)
2	133 (35%)	96 (38%)
3+	61 (16%)	41 (16%)
Family history of cancer <sup>b</sup>		
Yes	172 (45%)	112 (44%)
No	198 (52%)	140 (54%)
Unknown	10 (3%)	5 (2%)
Oral contraception usage during study period		
Continued	3 (1%)	2 (1%)
Stopped	88 (23%)	56 (22%)
Non-user	251 (66%)	174 (68%)
Unknown	38 (10%)	25 (10%)
Smoking status post chemotherapy		
Smoker	59 (16%)	37 (14%)
Ex smoker	23 (6%)	18 (7%)
Never-smoker	271 (71%)	184 (72%)
Unknown	27 (7%)	18 (7%)
Menopausal status post chemotherapy		
Amenorrhoeic	41 (11%)	19 (7%)
Pre menopausal	301 (79%)	214 (83%)
Unknown	38 (10%)	24 (9%)

<sup>a</sup> BMI = Body Mass Index.

<sup>b</sup> Family history = 1st or 2nd degree relative with breast cancer.

found between higher absolute and relative weight gain and a lower pathological stage at diagnosis ( $\rho = -0.12$ ;  $p = 0.05$ ). However, after adjusting for baseline BMI, pathological stage was found to be a significant independent predictor of absolute weight gain ( $p = 0.05$ ), but not relative weight gain ( $p = 0.14$ ).

Weight gain was not associated with age at diagnosis, use of oral contraception, smoking history, family history of breast cancer, parity or ethnicity. No association was found between weight gain and type or length of chemotherapy course, use of luteinising hormone releasing hormone agonists (LHRH), trastuzumab or adjuvant radiotherapy.

Forty-one of 345 (12%) patients in whom post chemotherapy menopausal status was known became amenorrhoeic during the study period. Mean weight gain in these patients (2.5 kg) was comparable to patients maintaining premenopausal status (2.9 kg;  $p = 0.74$ , Students t-test). Similarly, mean weight gain was not statistically different in patients who did or did not undergo surgical oophorectomy (0.8 kg v 1.8 kg respectively;  $p = 0.43$ ) or who received or did not receive ovarian irradiation (2.0 kg v 1.7 kg respectively;  $p = 0.62$ ). There was a weak negative association between duration of antiestrogen use and weight gain in the whole cohort ( $\rho = -0.14$ ;  $p = 0.03$ ) but this was not replicated in the 12-month cohort.

A total of 44% of women in this cohort aged 40y or younger were noted to have a post treatment waist circumference of greater than 88 cm, and 42% had a waist/hip ratio of  $>0.85$ . These values would place them in the highest risk category for obesity related comorbidity by the UK National Institute for Health and Clinical Excellence [16].

#### 4. Discussion

Although the relationship between chemotherapy use for breast cancer therapy and subsequent weight gain has been described previously, many of the populations studied have received chemotherapy regimens that would not be considered standard in current routine practice. This cohort allows us to study factors which may influence weight change in patients who have received modern day chemotherapy regimens (e.g. taxanes) and immunotherapy (e.g. trastuzumab).

Using multivariate analysis, the strongest predictor of significant weight gain in our cohort of patients was a lower pretreatment BMI. Women with low or low-normal BMI were the most likely to gain greater than 5% of their pretreatment weight. This level of weight increase may not necessarily place patients into “overweight” or “obese” morphological categories. Nevertheless, the negative impact of weight gain on overall survival and well-being following breast cancer diagnosis may still apply [4–6,17].

The finding that breast cancer patients with a lower pretreatment BMI are more likely to gain weight following therapy has been reported in other studies [12]. These data together confirm that approaches to maintain a stable weight through adjuvant chemotherapy should be discussed with healthy weight women, prior to commencement of treatment.

Previous reports have found larger weight gains with older regimens such as cyclophosphamide methotrexate 5-fluorouracil (CMF) compared to anthracyclines [3,18]. The majority of patients (95%) in our cohort of premenopausal UK patients received anthracycline with or without a taxane and we noted no association between taxane vs non taxane regimens or length of treatment, and weight gain. Antioestrogen therapy is not considered to be a significant factor for weight gain in breast cancer patients [19]. We found a weak negative association between length of antiestrogen treatment and weight gain in the whole cohort but this was not replicated in the 12-month cohort. This finding is possibly a statistical anomaly as our study may be underpowered to investigate this potential association.

An inverse association between cancer stage and weight gain was seen in our study population, which is consistent with the findings of the Nurses Health Study [20] and other trials [21]. Mechanisms for the greater weight gain amongst lower stage women remain unclear and require further study. However, it also potentially identifies a subset of women in whom weight control counselling may be of value.

Nearly half of our cohort of patients (44%) showed increased central obesity at 12-months as defined by the waist measurements of  $>88$  cm and waist/hip ratio of  $>0.85$  [16]. Increases in central obesity have been linked to poorer cancer outcomes [22] and increased risk of cardiovascular disease in breast cancer survivors [9].

Cessation of cigarette smoking has been shown in some studies to be associated with subsequent weight gain and this can be a confounding factor when examining weight changes in women diagnosed with breast cancer [23]. We found no differences in degree of weight gain between women who continued smoking during chemotherapy, those who ceased smoking and never smokers. The lack of relationship in our cohort most likely reflects low statistical power with a small group of ex-smokers (6%).

The strengths of our study are that it assesses weight change in a well-defined, cohort of patients, prospectively recruited, with administration of contemporary chemotherapy regimens. A large number of factors known to influence weight such as the use of oral contraception, treatment related variables such as type and duration of chemotherapy regimen, type of surgery and the use of endocrine or trastuzumab therapy were examined. Pre and post

**Table 2**  
Treatment related factors amongst women in the POSH weight gain sub-study.

	Whole cohort (n = 380)	12 months cohort (n = 257)
Pathological stage		
T0/TIS	12 (3%)	7 (3%)
T1	182 (48%)	129 (50%)
T2	158 (42%)	99 (38%)
T3	24 (6%)	18 (7%)
Unknown	4 (1%)	4 (2%)
Breast surgery		
BCS <sup>a</sup>	176 (47%)	115 (45%)
mastectomy	202 (53%)	141 (55%)
No surgery	2 (0.5%)	1 (0.5%)
Antioestrogen type		
AI <sup>b</sup>	13 (3%)	9 (4%)
Tamoxifen	246 (65%)	171 (66%)
None	121 (32%)	77 (30%)
Duration of antioestrogen use (days)		
median	202	188
range	1–3285	18–3485
Oophorectomy within study period	17 (4%)	7 (3%)
Ovarian irradiation within study period	101 (27%)	66 (26%)
Chemotherapy		
Adjuvant	325 (86%)	222 (86%)
Neoadjuvant	55 (14%)	35 (14%)
Chemotherapy type		
Non taxane	287 (76%)	195 (76%)
Taxane	93 (24%)	62 (24%)
Chemotherapy length (days)		
mean (s.d.)	129 (34)	129 (33)
range	21–259	21–259
LHRH <sup>c</sup> within study period	101 (27%)	66 (26%)
Trastuzumab within study period	92 (24%)	64 (25%)
Breast radiotherapy within study period	324 (85%)	220 (86%)

<sup>a</sup> BCS Breast Conserving Surgery.

<sup>b</sup> AI Aromatase Inhibitors.

<sup>c</sup> LHRH Luteinising Hormone Releasing Hormone agonists.

**Table 3**  
Weight gains and waist and hip measurements amongst premenopausal women in the POSH weight gain sub-study.

	Whole Cohort (n = 380)	12 months cohort (n = 257)
Pre-chemotherapy weight (kg)		
mean (s.d.)	71.3 (16.0)	70.4 (15.5)
range	44.4–136.8	44.4–121.0
Absolute weight gain per year (kg)		
mean (s.d.)	1.8 (4.9)	1.7 (4.8)
range	–22.1 - 22.7	–22.1 - 22.6
Relative weight gain per year		
mean (s.d.)	2.8% (7.0%)	2.8% (6.7%)
range	–18.9% - 35.7%	–18.9% - 33.3%
weight loss >5%	35 (9%)	22 (9%)
maintain weight (loss or gain <5%)	232 (61%)	154 (60%)
modest weight gain (≥5% & <10%)	60 (16%)	48 (19%)
large weight gain (≥10%)	53 (14%)	33 (13%)
Waist circumference (cm)		
mean (s.d.)	87.2 (13.6)	86.7 (12.8)
range	62.0–132.0	65.0–124.5
Waist: hip ratio mean (s.d.) range	0.83 (0.08) 0.64–1.21	0.83 (0.08) 0.64–1.21
No. of women with waist measurement ≥ 88 cm (%)	156 (41%)	113 (44%)
No. of women with waist: hip circumference ratio ≥ 0.85 (%)	163 (43%)	108 (42%)

**Table 4**  
Relative weight change per Body Mass Index (BMI) quartiles amongst premenopausal women in the POSH weight gain sub-study.

Whole cohort (n = 379)		12 months cohort (n = 257)	
BMI Quartile (kg/m <sup>2</sup> )	mean % weight gain per year	BMI Quartile (kg/m <sup>2</sup> )	mean % weight gain per year
<22.3	4.3%	<22.3	4.1%
22.3–24.9	3.3%	22.3–24.7	3.6%
24.9–28.8	2.8%	24.7 – <28.4	3.1%
≥28.8	0.8%	≥28.4	0.6%

chemotherapy weight measurements and post chemotherapy waist/hip measurements were measured by researchers using standardised methods [14] ensuring consistent data acquisition across the recruiting centres.

The weaknesses of the study include absence of comparative pre and post treatment waist/hip measurements or more detailed measures of changes in body composition after diagnosis for example percentage body fat, lean body mass and intramuscular fat which have been linked to cancer outcomes in patients with breast cancer [24]. Weight changes and waist measurements at 12-months were recorded only in a subset of 257 patients as the remaining 123 patients were measured outwith of this time frame. However, changes in weight were comparable between these whole and 12-month  $\pm$  3 months cohorts reflecting the previous finding that most weight gain occurs in the first year following diagnosis [25]. We did not have any record of corticosteroid administration during chemotherapy and therefore can make no assessment whether this may have influenced our findings. Also, the study was not powered to detect small, but clinically significant, influences of some parameters such as ethnicity, changes in smoking status or menopausal status on weight gain in our cohort of patients.

Although we found that patients with a lower baseline BMI and lower pathological stage gained most weight, a considerable amount of the weight increase was not explained by the parameters in our analysis. Further research is required to examine other factors which may be influential on weight gain in breast cancer survivors. For example, areas for investigation could include psychological and behavioural factors. The adoption of differing eating styles as changes in hunger patterns may influence weight gain and disinhibition with food following a cancer diagnosis may predict weight gain in previously restrained eaters [26]. Others have shown that a prediction model based on single nucleotide polymorphisms, age and BMI at diagnosis can potentially identify those breast cancer patients at high risk of post treatment weight gain [21].

Patients identified as high risk of developing breast cancer treatment related weight gain may potentially benefit from targeted interventions directed at modifying lifestyle factors which contribute to the weight increases. For example, interim results of the randomised phase III SUCCESS C study ([www.sabcs.org/SABCS/2018/AllAbstracts\\_2018-12-03\\_Updated.pdf](http://www.sabcs.org/SABCS/2018/AllAbstracts_2018-12-03_Updated.pdf)) have shown that a telephone based individualised lifestyle intervention program resulted in weight loss compared to a control group receiving generalised recommendations for a healthy lifestyle in whom weight gain was noted. This difference translated into improved disease free survival within the intervention group compared to the control group within a median follow up of 64 months. If these results are confirmed more widely then such lifestyle interventions could offer an opportune approach to weight control for women with early breast cancer.

We have shown that 30% of premenopausal women treated with chemotherapy for breast cancer gain clinically significant amounts of weight and that over 40% have central obesity 12-months following diagnosis. We have identified that low/normal pretreatment BMI is able predict weight gain in young (<40y) breast cancer patients. This group may potentially benefit from pretreatment counselling regarding weight control or post treatment dietary/exercise interventions in order to help improve longer term outcomes.

### Conflicts of interest

All authors confirm the absence of any conflict of interest in the contents of this manuscript.

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### Declaration of interest

None.

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