Weight change associated with anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer

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Abstract

Introduction: Weight gain is commonly reported by breast cancer patients on tamoxifen or aromatase inhibitors. Since weight gain may impact on outcome and compliance we have prospectively assessed the effects of these agents on weight change in three randomised trials for the treatment or prevention of breast cancer.

Methods: Data on weight change in postmenopausal women from three large clinical trials investigating endocrine therapy for the treatment or prevention of breast cancer were analysed (ATAC, IBIS-I, IBIS-II).

Results: In the IBIS-I study, mean weight change on tamoxifen was +0.1 kg (SD 0.1) compared with +0.3 kg (SD 0.1) in women taking the placebo (P=0.3) between baseline and 12 months of follow-up. In the IBIS-II trial, no statistically significant difference was found between anastrozole and placebo after 12 months of follow-up (+0.8 kg (SD 5.3) vs. +0.5 kg (SD 7.4), P=0.5). In the ATAC trial, no statistically significant differences in weight gain between anastrozole and tamoxifen were found after 12 months of follow-up (+1.4 kg (SD 3.9) vs. +1.5 kg (SD 4.0), P=0.4). Significant baseline predictors for gaining more than 5 kg of weight after 12 months of follow-up were: being younger than 60 years old, smoking, and mastectomy.

Conclusion: All three trials demonstrate that weight gain occurs primarily within the first 12 months of active treatment in a subset of patients. In the prevention trials, weight gain does not differ between anastrozole, tamoxifen and placebo and also did not differ between anastrozole and tamoxifen in the treatment trial.

Introduction

Weight gain is commonly reported by breast cancer patients after diagnosis. Gains are greatest amongst patients receiving adjuvant chemotherapy (3-7 kg) [1-3] and are on average more modest with adjuvant endocrine therapy (1-2 kg) [4]. However, subsets of patients gain a significant amount of weight on endocrine therapy [5]. Patients taking tamoxifen or anastrozole perceive these agents to cause weight gain, which is a major concern [6, 7] and may limit persistence to these agents. Excess weight at diagnosis [8, 9] and weight gain during treatment has been associated with an increased relapse rate and poorer survival [10-14].

Most reports on weight gain with tamoxifen [2, 15-17] do not have a no-treatment comparison group, making it difficult to attribute the weight gain entirely to tamoxifen. However, no weight gain with tamoxifen was observed in the NSABP-P1 study [18] and the Royal Marsden chemoprevention study [19]. There are even fewer data on weight change with the three major AIs (anastrozole, letrozole, and exemestane). In the adjuvant setting, the effects of AIs on weight gain have been reported compared to tamoxifen. The first report of the ATAC trial suggested no difference in weight gain between tamoxifen and anastrozole [20]. Furthermore, Francini *et al.* [21] reported no significant weight change with exemestane when given after 2 years of tamoxifen in postmenopausal women with early breast cancer.

AIs are being tested in the preventive setting in high risk women [22, 23]. These randomised controlled studies allow the effects of the AIs on weight change to be assessed independently from the effects of cancer diagnosis. In addition, they have the advantage of comparing an AI to a placebo and not tamoxifen as in most treatment trials. It is important to evaluate the association of AI treatment and weight change in both the adjuvant and preventive settings as weight gain may have adverse effects on the natural history of breast cancer [14]. Importantly, weight changes may have an impact on compliance, which is particularly important in the prevention setting [24], have an adverse effect on breast cancer risk [25] and outcome [26].

The objective of this study was to assess the effects of anastrozole on weight change in postmenopausal women compared to tamoxifen in the adjuvant setting (Anastrozole, Tamoxifen, Alone or in Combination (ATAC)) trial and to placebo in the International Breast cancer Intervention Study (IBIS-II) in the preventive setting. We also investigated weight change in the IBIS-I study, which compared tamoxifen with placebo in women at increased risk of breast cancer.

Methods

The IBIS-I trial is a double-blind randomised trial of women at high risk of developing breast cancer. Women were randomly allocated to either 5 years of tamoxifen (20 mg per day) or matching placebo, and were followed up every 6 months during the 5 years of treatment. Recruitment took place between April 1992 and March 2001. Additional details of patients are given in the main report [27]. Weight was measured at baseline, 12 months, and 5 years of follow-up. All postmenopausal women (placebo N=1922; tamoxifen N=1936) are included in this analysis. Baseline weight measurements were available for 1898 (98.0%) in the tamoxifen group and for 1885 (98.1%) in the placebo group. 1369 (70.7%) of women in the tamoxifen group had a baseline and 12 month weight measurement and a further 606 (31.3%) had a baseline, 12 and 60 month weight measurement available for analysis. In the placebo group, 1396 (72.6%) of women had a baseline and 12 month weight measurement whereas 648 (33.7%) women had a baseline, 12 and 60 month weight measurement. The IBIS-I trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN91879928.

The IBIS-II prevention study is randomising high risk postmenopausal women without breast cancer to receive either anastrozole 1 mg/day or matching placebo for 5 years. Weight information was collected at entry to the trial for all participants, but weight was only measured at follow-up visit for those who participated in the bone sub-study (anastrozole N=577; placebo N=568). Baseline weight measurements were available for 574 (99.5%) in the anastrozole group and 560 (98.6%) in the placebo group. 364 (63.1%) women in the anastrozole group had a baseline and 12 month measurement compared to 355 (62.5%) in the placebo group. Recruitment into this study is still ongoing. The IBIS-II trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN31488319.

The ATAC study is a double-blind randomised clinical trial in which postmenopausal women with early breast cancer were randomly assigned to receive oral daily anastrozole (1 mg) alone (N=3092), tamoxifen (20 mg) alone (N=3094), or the combination (N=3097) in a double blind fashion for five years after surgery. Recruitment in 21 countries took place between July 1996 and March 2000. Patients from the combination arm were discontinued after 33 months of follow-up and are not included in this analysis. Details of the trial design, methods, primary objectives, and major outcomes have been published previously [20, 28-30]. Weight was measured at baseline and at 6 monthly intervals thereafter for 5 years. Baseline weight measurements were available for 6069 (98.1%) women in the monotherapy arms; baseline and 12 month measurements for 5200 (84.1%) women, and baseline, 12 month and 60 month for 3285 (53.1%) women. The ATAC trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

For all trials, weight was measured at entry and any subsequent clinic visits by research staff and was not a self-reported measure. Weight was measured on digital and non-digital scales and participants wore light clothes but no shoes. Written informed consent was obtained from all participants before trial entry for each of these trials. The trials were performed in accordance with the Declaration of Helsinki (1996 revision) and under the principles of good clinical practice.

Sample means and standard deviations were computed to determine point estimates and variability of weight change as a continuous measure and proportions were calculated for categorical measures. The effect of the endocrine treatment on weight change was analysed by comparing the weight change of the anastrozole to either tamoxifen (ATAC) or placebo (IBIS-II). In IBIS-I, tamoxifen was compared to placebo. Mean weight changes within groups were assessed using the Student's t-test. Weight change categories were defined as follows: weight loss (losing more than 2 kg), stable weight (weight change between -2 kg and +2 kg), weight gain (gaining between 2 kg and 5 kg), and significant weight gain (more than 5 kg). For the ATAC and IBIS-I study potential risk factors for weight gain of more than 5 kg were analysed (age, HRT use, smoking status at entry (for both ATAC and IBIS-I), chemotherapy, radiotherapy, surgery, and region (United Kingdom, North America, Rest of the World) (for ATAC only)) via univariate and multivariate logistic regression. Interactions between treatment and sub-groups were based on likelihood ratio tests with an added interaction term. All P-values are two-sided and all confidence intervals are at the 95% level. All calculations were performed using STATA (Version 11.2).

Results

IBIS-I

A total of 2765 (71.7%) postmenopausal women had a baseline and 12 month weight measurement available. For 32.5% baseline, 12 month and 60 month weight measurements were available for analysis. The mean weight at baseline was 71.7 kg (SD 13.6) and was similar in both treatment arms (Table 1). After 12 months of follow-up, an increase of 0.9 kg was observed and no statistically significant difference was observed between treatment arms (P=0.07). The majority of women kept their weight stable (49.5%) after 12 months and changes were comparable between tamoxifen and placebo (Table 1). Similarly, for those with a 60 month weight measurement, the majority kept their weight stable but around 17.7% of women gained over 5 kg after 60 months of follow-up. Over the entire treatment period (baseline to 60 month), 35% of postmenopausal women kept their weight stable and 19% either lost more 2 kg or gained more than 5 kg (Table 1). Mean weight at baseline, 12 months, and 60 months of follow-up was comparable between treatment groups (Table 1).

We also investigated if age, smoking status and HRT at entry predicted weight gain over 5 kg after 12 months of follow-up. Only age was a significant factor, indicating that women under the age of 60 years gained significantly more than 5 kg of weight compared to their counterparts (Table 2). Women who were smokers at entry had a 29% higher relative risk of gaining more than 5 kg of weight but the difference was not statistically significant compared with non-smokers (Table 2). HRT use at entry did not have any impact on weight gain at 12 months of follow-up.

IBIS-II

For the IBIS-II trial baseline and 12 months weight measurements were available for 717 women (62.8%). The mean weight at baseline was 73.9 kg (SD 14.0) for women randomised to anastrozole and 75.5 kg (SD 15.9) for women in the placebo group (Table 3). After 12 months of follow-up, women in the anastrozole group had a mean weight gain of 0.8 kg (5.3) compared with 0.5 kg (7.3) in the placebo group (P=0.5). The majority of women (51.1%) were weight stable, 18.2% gained between 2 kg and 5 kg, and 9.1% gained more than 5 kg (Table 3). Importantly no statistically significant differences were found between anastrozole and placebo for any comparisons at any follow-up time. There is currently inadequate follow up to evaluate weight change at 60 months of follow-up.

ATAC trial

6186 postmenopausal women were randomised into the ATAC trial (anastrozole=3092, tamoxifen=3094). Of these, 5200 (84.1%) women had a baseline and 12 month weight measurement available. 2020 women had withdrawn from the study before 5 years of follow-up and for those no weight measurement at 60 months of follow-up was available. For a further 881 women no 60 months weight measurement was available although they have finished the 5 years of active follow-up. Therefore, 3285 (53.1%) women had a complete weight measurement set (baseline, 12 months, 60 months) available. There was no difference in missing 5 years values according to geographical region (data not shown). There was also no difference in the clinical characteristics of women with and without weight data.

After 12 months of follow-up the mean weight change was an increase of 1.4 kg and no statistically significant difference between treatment arms was found (Table 4). Between baseline and 12 months, a total of 45.4% women kept their weight stable, 14.8% lost more than 2 kg, 26.8% gained between 2 kg and 5 kg and 13.1% women gained more than 5 kg within the first 12 follow-up months (Table 4).

There was a mean weight loss of 0.35 kg at 60 months of follow-up with no significant changes in weight observed between 12 months and 60 months in either treatment arm. The majority of women either kept their weight stable or lost more than 2 kg of weight in this time period and only 11.5% gained more than 5 kg from 12 to 60 months (Table 4). Between baseline and 60 months of follow-up, approximately 31% kept their weight stable, 20% gained between 2-5 kg and 20% gained more than 5 kg in both treatment groups (Table 4). No significant differences between treatment arms were found at any follow-up point.

We investigated predictors at baseline for gaining more than 5 kg of weight in the first 12 months of follow-up. Being younger than 60 years old, smoking at entry, and having had a mastectomy were all statistically significant predictors in a univariate analysis. Women from the UK gained significantly more within the first 12 months of follow-up compared to those from the Rest of the World (Table 5), although baseline weights were similar (mean (SD) 69.8 kg (13.3) UK vs. 70.1 kg (12.9) Rest of the World). All these variables were still highly significant in the multivariate model (Table 5). Women who had radiotherapy as part of their initial breast cancer treatment gained significantly less weight at 12 months of follow-up compared with those not receiving radiotherapy (OR=0.73 (0.64-0.83)). We did not observe more significant weight gain over 5 kg for women who have had chemotherapy before study entry compared to those who had not previously received chemotherapy (Table 5).

Discussion

This retrospective analysis reports on weight change amongst postmenopausal women receiving anastrozole, tamoxifen, or placebo in three randomised trials. Weight gain during time on trial occurs in a sub-set of breast cancer patient (ATAC) receiving tamoxifen or anastrozole, but also among healthy postmenopausal women receiving tamoxifen, anastrozole or placebo in the preventive setting (IBIS-I, IBIS-II) and is apparently not influenced by treatment since similar changes are detected in women taking placebos. Weight gains were mainly confined to the first 12 months of follow-up with no significant weight change seen thereafter (ATAC, IBIS-I). This was also observed by Irwin et al. [5]. An important finding of this analysis is that those on placebo in the prevention trials gained similar amount of weight as those on either anastrozole or tamoxifen and thus weight change is unlikely to be caused by the endocrine therapies used.

We did not find a statistically significant difference between either anastrozole or tamoxifen and placebo in terms of weight gain at either baseline, 12 or 60 months of follow-up. Similar results were reported by the Royal Marsden collaborators who also saw no difference in weight gain between those randomised to tamoxifen and placebo [31]. In both the IBIS-I and IBIS-II trials, women taking placebo gained similar amount of weight indicating that endocrine therapy may not be solely responsible for weight gain in postmenopausal women at high risk of developing breast cancer.

Weight gain in the first 12 month of follow-up was greater in the adjuvant setting compared to the preventive setting and suggests that since there was no difference between treatment and placebo in the prevention trials, that other physical and psychological manifestations surrounding the diagnosis may be responsible for weight gain. Body weight and weight changes are determined by a range of factors such as calorie intake, physical activity, metabolic rate, and psycho-social factors [32, 33]. Women with breast cancer who undergo treatment may be more susceptible to emotional disturbance anxiety and depression which may influence eating and exercise patterns [32, 34]. Decreased physical activity [35], fatigue [36], and hormonal changes [37] have been reported in this group of women. However, between 12 and 60 months of follow-up 32.5% of women in the ATAC trial lost more than 2 kg of weight so that by 5 years of follow-up women on average lost weight compared to the 12 month value (Table 4). This suggests that 5 years after breast cancer diagnosis women have adjusted to their life with breast cancer and lost much of the weight which they had initially gained during the first year post diagnosis.

In the ATAC trial, a greater weight increase was observed in women under the age of 60. Postmenopausal women in the IBIS-I trial who were under the age of 60 also gained significantly more weight than older women. Wing and colleagues [38, 39] reported on weight gain in healthy premenopausal women and found that weight gain is more closely related to age than menopausal status. We have not observed a significant weight gain for those who had chemotherapy before study entry in either treatment group in the ATAC trial. This may be explained by the fact that surgery and chemotherapy had to be completed before randomisation took place. We did not collect weight at diagnosis and therefore can not interpret weight change between diagnosis and study entry.

Significant weight gain was observed for those who had undergone a mastectomy, but no radiotherapy, which may reflect greater rehabilitation, decreased physical activity, and increased anxiety amongst women undergoing more complicated surgery. Radiotherapy is associated with weight loss mainly due to nausea or problems with eating [40-42]. In the ATAC trial, women were allowed to undergo radiotherapy for their primary breast cancer whilst being randomised to the study and this may explain why we see some weight loss in those who are or were on radiotherapy after 12 months of follow-up. Non-smokers at entry did not gain significantly more weight than smokers. However, we do not have data on how many of the previous smokers stopped smoking and therefore gained weight, since this may be an explanation for this finding. Similar results although not significant were seen in the IBIS-I trial, in which smokers also gained more than 5 kg of weight after 12 months compared to their counterparts.

Changes in weight, specifically weight gain, may affect drug persistence and therefore limit the overall effectiveness of the treatment. This problem is quite often observed with psychotropic drugs [43] and with diabetic patients [44] but there are some reports on the influence of weight gain and drug persistence in breast cancer patients mostly from population base studies. In the ATAC trial, 5.8% of patients chose to stop with the trial prematurely but we do not know the specific reasons for this and it is possible that some of the patients will have stopped due to weight gain. Drug persistence is important and has direct implications on breast cancer survival. We will address compliance and drug persistence in clinical trials in a separate analysis.

A main strength of our study is the large data sets for which weight at baseline and follow-up periods have been collected prospectively by trained research nurses rather than self reports. However, a limitation of this analysis is the completeness of the data. For the ATAC and IBIS-I study we have 50% and 30%, respectively, datasets with full weight information, which is in part due to missing weight but also due to drop-outs from the studies. Therefore, our 60 month data may be an underestimate of the number of women who gain weight long-term. A further limitation is that we have only monitored weight, which is a poor measure of body fat and muscle mass, especially in postmenopausal women. Previously published results on prospective changes in weight and body composition amongst 23 ATAC patients showed that significant gains in general and central fat and reduction in lean tissue were not reflected by their modest weight change [45].

In conclusion, our data do not support an independent effect of anastrozole or tamoxifen on weight change. In fact, weight gain was also observed in those randomised to placebo in the preventive setting. There is need to collect reliable weight data within treatment and prevention trials, which the IBIS-II trial will add information once longer follow-up is achieved. Ideally, trials should include prospective assessments of change in body composition, which is currently being investigated in a sub-set of participants in the IBIS-II trial.

Conflict of interest

Ivana Sestak, Michelle Harvie and Anthony Howell have no conflict of interest to declare. Jack Cuzick received research funding from AstraZeneca. John F. Forbes received honoraria from AstraZeneca and Novartis. Mitch Dowsett received consultancy fees, honoraria, research funding, and expert testimony from AstraZeneca.

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Table 1: Mean weight kg (SD) at baseline, follow-up months, and weight changes during follow-up according to treatment arm in the IBIS-I trial.

	Tamoxifen	Placebo	P-value
Baseline	N=1898	N=1885	
Mean weight, kg (SD)	71.9 (13.9)	71.4 (13.3)	0.3
12 month	N=1369	N=1396	
Mean weight change, kg (SD)	0.9 (1.4)	1.0 (1.5)	0.07
Weight change (Baseline – 12 month)			
Loss (>2 kg)	27.8%	25.0%	0.1
Stable (-2 kg to +2 kg)	49.3%	49.6%	0.9
Gain (2 kg to 5 kg)	15.9%	17.7%	0.2
Severe gain (>5 kg)	7.0%	7.7%	0.5
60 month	N=606	N=648	
Mean weight change, kg (SD)	1.3 (5.6)	1.3 (5.7)	0.9
Weight change (12 month – 60 month)			
Loss (>2 kg)	24.6%	27.2%	0.3
Stable (-2 kg to +2 kg)	38.5%	35.0%	0.2
Gain (2 kg to 5 kg)	19.3%	20.2%	0.7
Severe gain (>5 kg)	17.7%	17.6%	0.9
Weight change (Baseline – 60 month)			
Loss (>2 kg)	19.3%	19.5%	0.9
Stable (-2 kg to +2 kg)	34.4%	36.8%	0.3
Gain (2 kg to 5 kg)	21.0%	18.9%	0.3
Severe gain (> 5 kg)	19.9%	19.3%	0.7

Table 2: Predictors of weight gain (more than 5 kg) after 12 months of follow-up in the IBIS-I trial.

Variable	Mean change, kg (SD)	Gain >5 kg (%)	OR (95% CI)
Age group (years)			
<50 (N=2149)	0.07 (0.34)	6.1	Reference
50-60 (N=943)	0.05 (0.26)	4.6	0.73 (0.52-1.04)
>60 (N=773)	0.04 (0.24)	4.0	0.64 (0.43-0.96)
Prior HRT*			
No (N=1425)	0.05 (0.22)	4.9	Reference
Yes (N=1548)	0.06 (0.23)	5.8	1.18 (0.86-1.63)
Ex (N=885)	0.05 (0.22)	5.2	1.06 (0.72-1.55)
Smoking			
No (N=1926)	0.05 (0.22)	5.1	Reference
Yes (N=663)	0.06 (0.25)	6.5	1.29 (0.89-1.87)
Ex (N=1269)	0.05 (0.22)	5.0	0.99 (0.72-1.37)

*****HRT=Hormone replacement therapy

Table 3: Mean weight kg (SD) at baseline, follow-up months, and weight changes during follow-up according to treatment arm in the IBIS-II trial.

	Anastrozole	**Placebo**	**P-value**
Baseline	N=574	N=560	
Mean weight, kg (SD)	73.9 (14.0)	75.5 (15.9)	0.07
12 month	N=364	N=355	
Mean weight change, kg (SD)	0.8 (5.3)	0.5 (7.3)	0.5
Weight change (Baseline – 12 month)			
Loss (>2 kg)	22.3%	21.1%	0.7
Stable (-2 kg to +2 kg)	49.7%	52.4%	0.5
Gain (2 kg to 5 kg)	18.1%	18.3%	0.9
Severe gain (>5 kg)	9.9%	8.2%	0.4

Table 4: Mean weight kg (SD) at baseline, follow-up months, and weight changes during follow-up according to treatment arm in the ATAC trial.

	Anastrozole	Tamoxifen	P-value
Baseline	N=3030	N=3039	
Mean weight, kg (SD)	70.8 (14.0)	71.0 (14.2)	0.5
12 month	N=2614	N=2586	
Mean weight change, kg (SD)	1.4 (3.9)	1.5 (4.0)	0.4
Weight change (Baseline – 12 month)			
Loss (>2 kg)	15.4%	14.2%	0.2
Stable (-2 kg to +2 kg)	45.7%	45.1%	0.7
Gain (2 kg to 5 kg)	26.7%	26.8%	0.9
Severe gain (>5 kg)	12.2%	13.9%	0.07
60 month	N=1718	N=1567	
Mean weight change, kg (SD)	-0.3 (5.5)	-0.4 (5.5)	0.5
Weight change (12 month – 60 month)			
Loss (>2 kg)	32.6%	32.3%	0.1
Stable (-2 kg to +2 kg)	38.3%	37.0%	0.4
Gain (2 kg to 5 kg)	17.4%	16.6%	0.6
Severe gain (>5 kg)	11.8%	11.1%	0.6
Weight change (Baseline – 60 month)			
Loss (>2 kg)	26.8%	26.9%	0.9
Stable (-2 kg to +2 kg)	31.2%	31.0%	0.9
Gain (2 kg to 5 kg)	20.8%	20.0%	0.6
Severe gain (>5 kg)	21.2%	22.2%	0.5

Table 5: Predictors of weight gain (more than 5 kg) after 12 months of follow-up in the ATAC trial.

Variable	Mean change, kg (SD)	Gain over 5 kg (%)	Univariate model OR (95% CI)	Multivariate model OR (95% CI)
Age group (years)				
<60 (N=2192)	0.15 (0.35)	14.7	Reference	Reference
60-70 (N=2328)	0.10 (0.30)	10.1	0.65 (0.54-0.78)	0.64 (0.53-0.76)
<70 (N=1665)	0.08 (0.28)	8.3	0.52 (0.43-0.65)	0.49 (0.39-0.60)
Prior HRT*				
No (N=3979)	0.11 (0.32)	11.2	Reference	
Yes (N=2206)	0.11 (0.32)	11.2	1.00 (0.84-1.17)	-
Chemotherapy				
No (N=4849)	0.11 (0.31)	11.0	Reference	
Yes (N=1336)	0.12 (0.33)	12.1	1.11 (0.92-1.34)	-
Radiotherapy				
No (N=2296)	0.14 (0.34)	13.6	Reference	Reference
Yes (N=3889)	0.09 (0.30)	9.8	0.69 (0.59-0.81)	0.85 (0.68-1.06)
Smoking				
No (N=3667)	0.10 (0.30)	10.1	Reference	Reference
Yes (N=2510)	0.13 (0.34)	12.9	1.32 (1.12-1.55)	1.22 (1.03-1.44)
Surgery				
Wide local excision (N=3241)	0.09 (0.29)	9.2	Reference	Reference
Mastectomy (N=2944)	0.13 (0.34)	13.5	1.54 (1.32-1.81)	1.53 (1.23-1.91)
Region#				
UK (N=2131)	0.13 (0.33)	12.7	Reference	Reference
Rest of the World (N=2171)	0.10 (0.30)	10.2	0.78 (0.65-0.94)	0.80 (0.65-0.97)
North America (N=1883)	0.11 (0.31)	10.7	0.82 (0.68-1.00)	0.82 (0.67-1.00)

*****HRT=Hormone replacement therapy, # UK= United Kingdom, North America = United States and Canada