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Original article

Tamoxifen related side effects and their impact on breast cancer incidence: A retrospective analysis of the randomised IBIS-I trial

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ABSTRACT

Background: Studies in the adjuvant setting have shown that endocrine therapy related side effects predict breast cancer recurrence risk. Here, we assess the relationship between early reported side effects and incidence of breast cancer in women randomised to tamoxifen for cancer prevention in the International Breast Intervention Study (IBIS)–I trial.

Methods: Women randomised to tamoxifen in the IBIS-I trial and for whom side effect status was known at the 6-month follow-up visit were included in this analysis. Side effects included in this analysis were hot flushes, vaginal discharge, and vaginal dryness. The primary endpoint was all breast cancer and secondary endpoint was oestrogen receptor (ER) positive breast cancer. Cox proportional hazard models were used to investigate breast cancer incidence in the tamoxifen group with and without side effects reported within 6 months of randomisation.

Results: Women randomised to tamoxifen and reporting hot flushes at the 6-month follow-up visit had a non-statistically significant increase in breast cancer compared to those without hot flushes (HR = 1.26 (0.98–1.62), P = 0.08). A significant higher breast cancer risk was observed for postmenopausal women who reported hot flushes at the 6-month follow-up visit compared to those without hot flushes (HR = 1.59 (1.12–2.26), P = 0.01). A higher risk was observed for ER-positive breast cancer in postmenopausal women (HR = 1.81 (1.19–2.74), P = 0.01). No significant associations between gynaecological side effects and breast cancer occurrence was observed.

Conclusions: Overall, no association between side effects reported at 6 months and subsequent breast cancer occurrence was observed. Some side effects might be useful markers for breast cancer occurrence in postmenopausal women.

1. Introduction

For women at high-risk of breast cancer, 5-years of preventive endocrine therapy can be used to reduce breast cancer risk [1–4]. Prevention trials with selective estrogen receptor modulators (SERMs), such as tamoxifen, demonstrate a reduction in overall breast cancer incidence of 38% with a reduction of 51% for estrogen receptor (ER)-positive invasive disease alone [1]. The preventive effects of tamoxifen last well beyond the active treatment phase, suggesting at least 20 years of benefit from five years of active preventive therapy with tamoxifen [5].

Despite these benefits, less than 15% of eligible women choose to take preventive therapy, with fear of side effects cited as a major cause behind the limited uptake [6,7]. Women often believe that the risks associated with SERMs outweigh the benefits [8]. An increased incidence of gynaecological side effects, hot flushes, venous thromboembolic events, and endometrial cancers have all been associated with tamoxifen use [9,10]. However, these side effects only persist during the active phase of the trial, and subside after the treatment phase and are not increased in the follow up period [11,12].

Sex hormone concentrations have been hypothesised to cause the side effects commonly observed as a result of taking endocrine therapy [13–15]. In postmenopausal women, oestradiol, testosterone, sex hormone binding globulin (SHBG) and dehydroepiandrosterone sulphate (DHEA-S) may contribute to the pathogenesis

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Table 1
Baseline characteristics according to randomised treatment. IQR=Interquartile Range, BMI=Body Mass Index, kg = kilogram, m = meter, HRT=Hormone Replacement Therapy.

	Placebo (N = 3384)		Tamoxifen (N = 3341)	
Breast cancers	378 (11.2%)		272 (8.1%)	
Median follow up (years), (IQR)	16.6 (14.8–18.2)		16.7 (14.9–18.3)	
Median age (years), (IQR)	49.0 (46.0–55.0)		49.0 (46.0–55.0)	
Menopausal Status				
Premenopausal	1551	(45.8%)	1512	(45.3%)
Postmenopausal	1819	(53.8%)	1806	(54.1%)
BMI (kg/m^2)				
<25	1363	(40.3%)	1346	(40.3%)
25-30	1256	(37.1%)	1211	(36.2%)
>30	765	(22.6%)	784	(23.5%)
HRT Use				
Never	2023	(59.8%)	1962	(58.7%)
Current	887	(26.2%)	835	(25.0%)
Ex-User	472	(13.9%)	538	(16.1%)

of breast cancer and the occurrence of side effects [16]. Oestrogens, in particular, are often associated with the onset of hot flushes as shown by multiple breast cancer prevention trials using SERMs to stop circulating oestrogens binding with oestrogen receptors to prevent breast cancer [9,17].

However, oestrogen reduction alone may not explain the occurrence of hot flushes as there is no relationship between vaginal, urinary or circulatory concentrations of oestrogen in women with and without hot flushes [18]. Association between sex hormones and hot flushes shows that there was no significant difference in the concentrations of oestradiol, testosterone or SHBG between women who report symptoms versus not. However, significant differences in the concentrations of DHEA-S were observed between those reporting symptoms compared to those without these symptoms [19]. DHEA has shown to reduce hot flushes by 50% in postmenopausal women with a history of breast cancer suggesting that androgens may also play a role in hot flushes [20]. Tamoxifen has been found to have a significant impact on incidence of gynaecological symptoms largely due to its influence blocking circulating oestrogens. In adjuvant trials, aromatase inhibitors (AIs) have been found to cause more vaginal dryness than tamoxifen, which increases both vaginal discharge and irregular bleeding. This suggests two different mechanisms between tamoxifen and AIs in the vaginal tract [21,22].

Side effects of endocrine therapy are associated with a decrease in adherence to therapy, which has been shown to reduce the benefit gained from taking endocrine therapy [7,23,24]. However, they may play an important indirect role in breast cancer prevention. Studies in the adjuvant setting have shown that endocrine therapy related side effects are associated with a reduction in breast cancer recurrence [25–29], which suggests that side effects might be a marker for predicting therapy benefit [30].

The Women's Healthy Eating and Living (WHEL) trial reported that women with breast cancer experiencing hot flushes at baseline, and who were taking tamoxifen, were less likely to have a recurrence, compared to those that did not report these symptoms [25]. Women taking tamoxifen as part of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial reported that early joint related symptoms with or without vasomotor symptoms were associated with a greater decrease in breast cancer recurrence compared to no symptoms [26]. Fontein et al. found similar effects in the tamoxifen, exemestane adjuvant multinational (TEAM) trial [27] where a reduction in hormone receptor positive breast cancer events was observed in those reporting vasomotor symptoms. Lastly, results from the Breast International Group (BIG) 1–98 trial

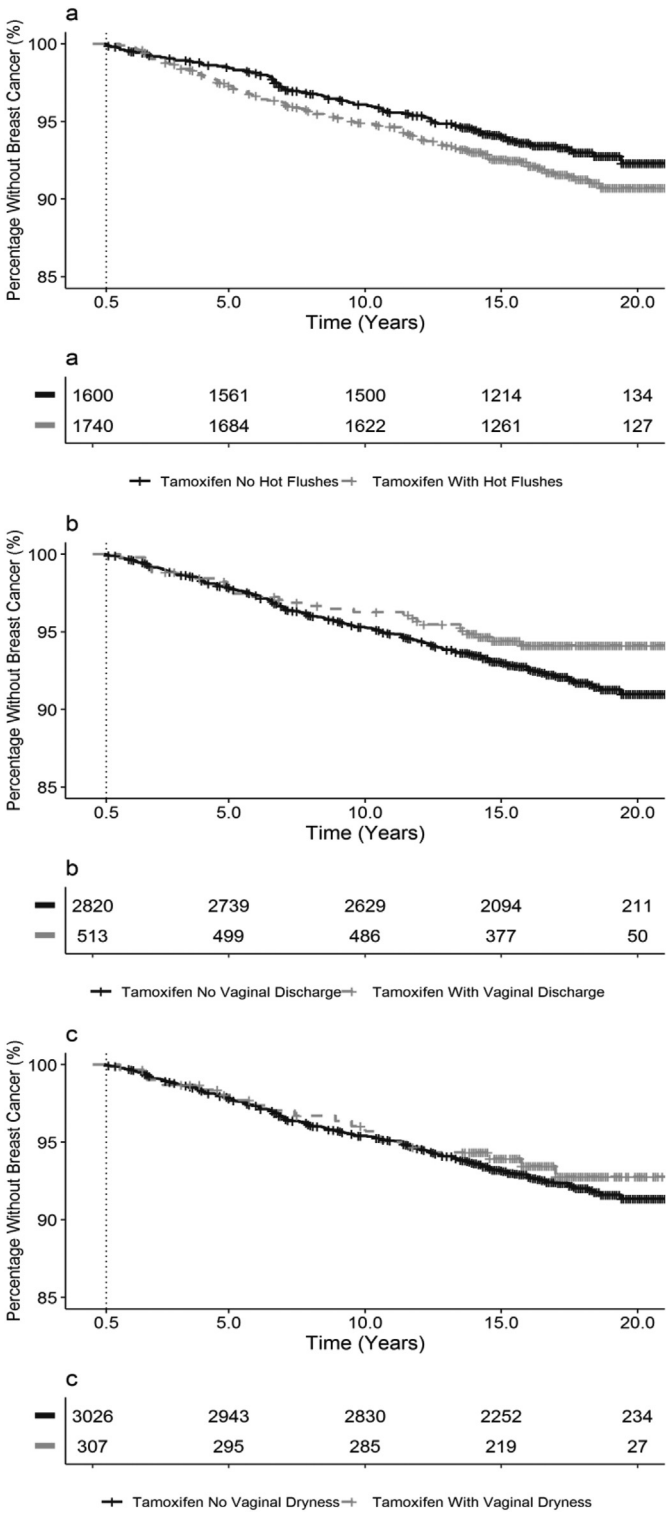

Fig. 1. Kaplan-Meier graphs for breast cancer incidence in the tamoxifen arm with and without side effects. A – Hot flushes, B – Vaginal discharge, C – Vaginal dryness.

support these findings where a 18% reduction in recurrence in postmenopausal women was observed when reporting vasomotor symptoms [28].

Here, we investigate whether occurrence of hot flushes, vaginal discharge, and vaginal dryness reported within 6 months of starting tamoxifen can be used to predict breast cancer incidence. These

Table 2
Hazard Ratios for all breast cancer incidence in the tamoxifen arm according to side effects at 6 months and menopausal status.

Side effect status	Overall		Postmenopausal		Premenopausal	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Hot flushes						
No	Reference		Reference		Reference	
Yes	1.26 (0.98–1.62)	0.08	1.59 (1.12–2.26)	0.01	0.89 (0.61–1.32)	0.57
Vaginal discharge						
No	Reference		Reference		Reference	
Yes	0.73 (0.49–1.07)	0.11	0.63 (0.38–1.07)	0.09	0.86 (0.48–1.55)	0.62
Vaginal dryness						
No	Reference		Reference		Reference	
Yes	0.88 (0.56–1.40)	0.59	0.89 (0.50–1.58)	0.70	0.84 (0.39–1.82)	0.66

symptoms are likely to be linked to mechanisms of drug metabolism, the effect of an oestrogen deficient environment or the agonist or antagonist effects of tamoxifen. Therefore, these side effects could be used as markers to assess tamoxifen efficacy.

2. Materials and methods

2.1. Study population

We analysed data from the double-blinded, randomised, placebo-controlled IBIS-I trial. A total of 7154 women were randomised to placebo (N = 3575) or tamoxifen (N = 3579) for five years and were followed up every six months during the active treatment period. Details of the trial design, methodology and primary outcomes have been published elsewhere [1,5,11]. The cut-off date for this analysis was the May 1, 2014 in line with previously reported long-term follow up of IBIS-I and events occurring after this date were not included [5]. The trial was performed in accordance with the Declaration of Helsinki (Third revision (1989)) and under the principle of good clinical practice. Trial registration: ISRCTN, ISRCTN91879928.

The primary objective of this analysis was to investigate whether side effects reported by women randomised to tamoxifen during the first 6 months are predictive of breast cancer occurrence. Here, we focus on hot flushes, vaginal discharge and vaginal dryness as these are the most common side effects associated with tamoxifen [31]. Side effects at the 6-month visit were assessed, using a structured case report form, during a clinical visit or telephone call. Women were asked about pre-defined symptoms, such as hot flushes and gynaecological symptoms. We included all whose side effect status was known and who did not develop breast cancer before the 6 month follow up point. 12 women who developed breast cancer, and 417 women had missing side effect status 6 months after randomisation and were excluded, leaving 6725 women for this analysis.

Secondary objectives included the analysis of side effects and breast cancer incidence according to menopausal status. Women with unknown menopausal status were excluded from this analysis (N = 44). Postmenopausal women were classified as newly menopausal if time between menopause and randomisation was 5 years or less, menopausal for 5–10 years, or greater than 10 years postmenopausal. Of the 1806 women on tamoxifen who were postmenopausal, 487 women had been postmenopausal for less than 5 years, 414 women have been postmenopausal for 5–10 years and 450 women postmenopausal for greater than 10 years at study entry. Time since menopause was unknown for 455 women. Finally, we assessed the association between side effects and breast cancer occurrence in those randomised to placebo and the overall IBIS-I population.

The primary endpoint was breast cancer (invasive and ductal carcinoma in situ) and a secondary endpoint was ER-positive breast cancer. Follow-up time was calculated from time of randomisation to breast cancer event, death, or final follow-up date. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for associations between side effects and breast cancer incidence. Chi-squared tests were used to assess the heterogeneity between subgroups. A secondary endpoint was ER-positive breast cancer. All P-values are two-sided. All analyses were performed using R project Version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

2.2. Ethics approval and consent to participate

The IBIS-I trial was approved by local ethics committees for each participating centre. All participants provided written informed consent, after an initial discussion with their IBIS-I doctor and a consideration period of at least 24 h.

Trial registration: ISRCTN, ISRCTN91879928.

3. Results

Baseline characteristics were evenly distributed between the two treatment arms and are shown in Table 1. Median follow up time was 16.6 years (IQR 14.8–18.2) and median age was 49.0 (IQR 46.0–55.0). 53.9% of women were postmenopausal, 59.3% never used hormone replacement therapy before trial entry, and 50.7% were never smokers (Table 1).

39.4% (N = 2647) women experienced hot flushes within the first six months and 22.1% (N = 1487) women experienced gynaecological symptoms. Women randomised to tamoxifen reported an approximate three-fold increase in the odds of reporting hot flushes during the first 6 months (tamoxifen = 1740 vs. placebo = 907, OR = 2.97 (2.68–3.29), P < 0.01). An approximate 3.5-fold increase in vaginal discharge (513 vs. 162, OR = 3.61 (3.00–4.34), P < 0.01) and a 20% increase in vaginal dryness (308 vs. 258, OR = 1.23 (1.04–1.46), P = 0.02) were reported at the 6 months visit by women randomised to tamoxifen when compared to placebo.

3.1. Side effects and breast cancer outcome in the tamoxifen group

No significant effect of hot flushes for the prediction of breast cancer was observed when compared to women not reporting these symptoms at the 6-month visit (HR = 1.26 (0.98–1.62), P = 0.08) (Fig. 1, Table 2). Similarly, no significant difference in breast cancer incidence was observed in women who reported vaginal discharge (HR = 0.73 (0.49–1.07), P = 0.11) or vaginal dryness (HR = 0.88 (0.56–1.40), P = 0.59) at 6 months compared to

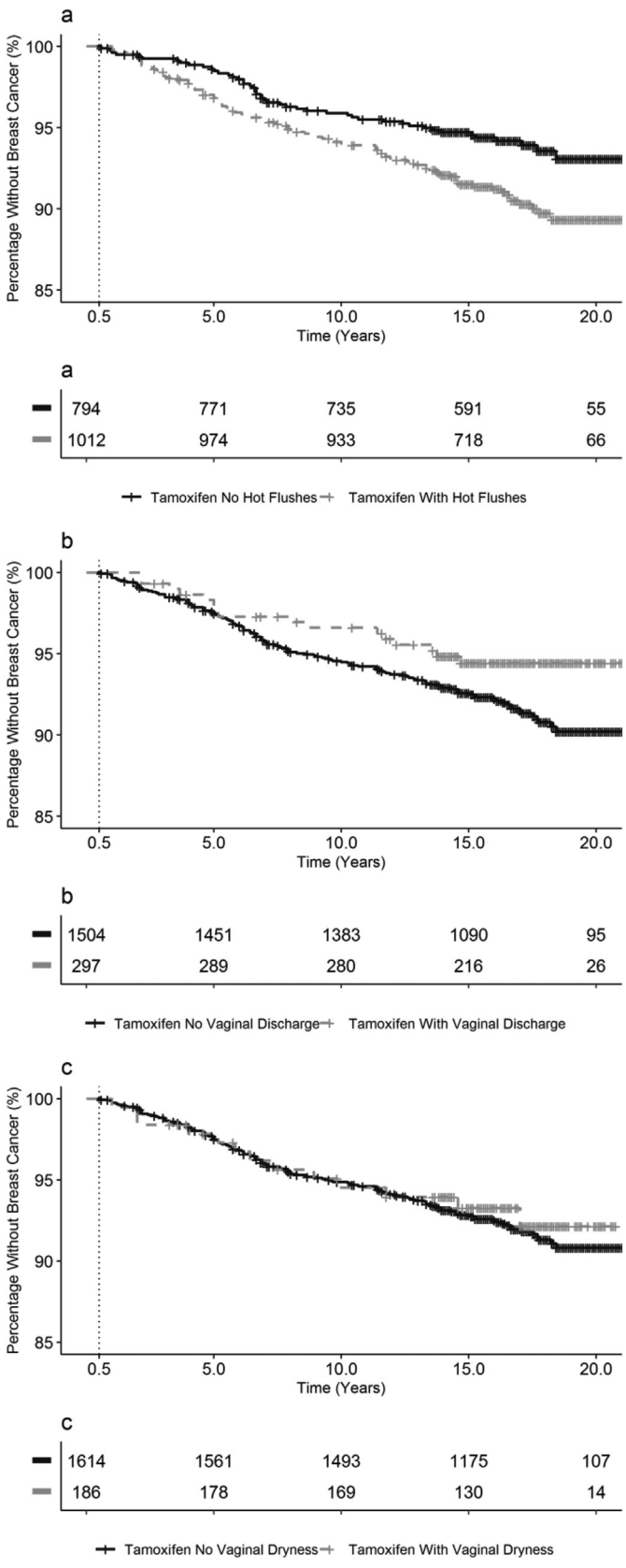

Fig. 2. Kaplan-Meier graphs for breast cancer incidence in the tamoxifen arm with and without side effects in postmenopausal women. A – Hot flushes, B – Vaginal discharge, C – Vaginal dryness.

those without these symptoms (Fig. 1, Table 2).

Postmenopausal women who reported hot flushes at 6 months had a statistically significant increase in breast cancer compared to those without hot flushes (HR = 1.59 (1.12–2.26), P = 0.01) (Fig. 2, Table 2). Neither gynaecological symptom predicted breast cancer incidence in postmenopausal women (vaginal discharge: HR = 0.63 (0.38–1.07), P = 0.09; vaginal dryness: HR = 0.89 (0.50–1.58), P = 0.70) (Fig. 2, Table 2). No association between hot flushes and breast cancer was observed for premenopausal women (HR = 0.89 (0.61–1.32), P = 0.57) (Table 2). Similarly, vaginal discharge and vaginal dryness were not predictive of breast cancer compared to those not reporting these symptoms (Table 2).

A secondary endpoint of our analysis was ER-positive breast cancer. Women reporting hot flushes had a statistically significant 38% increase in ER-positive breast cancer compared to those without hot flushes at 6 months (HR = 1.38 (1.04–1.85), P = 0.03) (Table 3). We observed a similar association between hot flushes and ER-positive breast cancer in postmenopausal women, but not significant effects were seen in premenopausal women (Table 3). Women reporting either vaginal discharge or vaginal dryness had a non-significant decrease in ER-positive breast cancer compared to those not reporting this symptom (Table 3). Similar results observed according to menopausal status (Table 3). A test for heterogeneity between menopausal status and any side effect was not significant (all $P_{heterogeneity} > 0.05$).

3.2. Side effects and breast cancer outcome time since menopause

Women on tamoxifen who were postmenopausal for less than 5 years before randomisation had a non-significant increase in all breast cancers (HR = 1.90 (0.90–4.03), P = 0.09) and an almost 3-fold increase in ER-positive breast cancer (HR = 2.80 (1.15–6.78), P = 0.02) if they reported symptoms at the 6-month follow-up visit. However, in women who were postmenopausal for more than 5 years before randomisation, no association between side effects and breast cancer outcome was observed. No association between gynaecological side effect and time since menopause was observed (data not shown).

4. Discussion

Here, we present results from a retrospective analysis of the IBIS-I trial, investigating whether endocrine symptoms reported by women randomised to tamoxifen were predictive of breast cancer occurrence. Our findings suggest that early reported symptoms do not predict breast cancer occurrence. However, we observed a significant inverse association between hot flushes and ER-positive breast cancer, specifically in postmenopausal women. Although there is no comparable data in the prevention setting, this finding is consistent with findings in the adjuvant setting [32]. Chlebowski et al. [32] analysed data of postmenopausal women in the Women's Health Initiative and found that those with vasomotor symptoms, particularly persistent vasomotor symptoms, were more likely to develop breast cancer than those not reporting these symptoms. However, our results are in contrast to a previous study by Mortimer et al. [25], which found that self-reported hot flushes were predictive of tamoxifen efficacy and long-term survival in women with early stage breast cancer. Additionally in the ATAC trial, the difference in breast cancer recurrence in patients reporting vasomotor symptoms compared to women without vasomotor symptoms was small and of borderline significance overall [26]. Observational studies have found conflicting results where vasomotor symptoms were associated with a decrease in breast cancer

Table 3
Hazard Ratios for ER-positive breast cancer incidence in the tamoxifen arm according to side effects at 6 months and menopausal status.

Side effect status	Overall		Postmenopausal		Premenopausal	
	HR (95%CI)	P-value	HR (95%CI)	P-value	HR (95%CI)	P-value
Hot flushes						
No	Reference		Reference		Reference	
Yes	1.38 (1.04–1.85)	0.03	1.81 (1.19–2.74)	0.01	1.01 (0.66–1.55)	0.96
Vaginal discharge						
No	Reference		Reference		Reference	
Yes	0.68 (0.43–1.06)	0.09	0.64 (0.35–1.17)	0.15	0.72 (0.36–1.44)	0.35
Vaginal dryness						
No	Reference		Reference		Reference	
Yes	0.92 (0.55–1.54)	0.75	0.84 (0.42–1.66)	0.61	1.04 (0.45–2.26)	0.92

HR = Hazard Ratio, CI = Confidence Interval.

incidence in two case-control studies and one cohort study [33–35] but no association was observed in a second cohort study [36].

Our results show no evidence of an association between hot flushes and breast cancer incidence in premenopausal women. This agrees with a study by Van den Berg et al. [27] where no association between hot flushes and breast cancer was observed in premenopausal women. We have previously established that side effects are a major reason for non-adherence to endocrine therapy [37]. 63.9% of women enrolled on IBIS-I were adherent to the full 5-years of endocrine therapy [11]. Women who experience a larger number or higher severity of side effects could be more likely to be non-adherent to endocrine therapy and therefore breast cancer risk may be higher than those who continue on therapy. Whilst the issue of adherence was not the focus of this analysis, further studies investigating the impact of adherence on breast cancer outcomes in women who experience side effects should be performed.

No significant effects were observed for the association between either of the gynaecological symptoms and breast cancer incidence. Since oestrogen is vital for the maintenance of vaginal epithelium and underlying tissues, without it the epithelium can thin resulting in dryness, discomfort and possible bleeding [38]. It is possible that tamoxifen provides a pseudo-estrogenic effect on the vagina increasing secretions without the presence of oestrogen. The incidence of vaginal discharge may represent the successful conversion of tamoxifen too more potent metabolites and thus a better breast cancer outcome. Conversely, vaginal dryness would suggest that there is little estrogenic action of tamoxifen on the vagina translating to a lack of efficacy of tamoxifen and no reduction in breast cancer incidence. Strengths of this analysis are that we are among the first to report in detail on the relationship between side effects and breast cancer incidence in the preventive setting. Data used for this analysis comes from a large clinical placebo-controlled trial with long-term follow-up and detailed information on breast cancer outcomes and side effects at each 6-monthly follow-up visit. This analysis focused on the relationship between early reported side effects and breast cancer incidence because the vast majority of side effects are reported within the first 6 months. Limitations include that side effects were all self-reported and they were also predefined based on previously established toxicity outcomes. However, we focused our analysis on the most common tamoxifen related side effects and believe that these are suitable markers for treatment efficacy. Additionally, symptoms prior to study entry were unknown and could not be accounted for in this study. Whilst adherence to therapy was known at the 6-month follow-up, we have not assessed full 5-year adherence and breast cancer outcome. In addition, we were not able to investigate the association of concurrent medication for symptoms relief and breast cancer outcome.

5. Conclusions

Our data suggests a weak association between hot flushes and overall breast cancer outcome for women on tamoxifen, but a strong association was observed for older, postmenopausal women. In particular a significant increase in ER-positive breast cancer was observed if women were postmenopausal for less than 5 years before study entry. Our results show that gynaecological symptoms are not good markers for prediction of subsequent breast cancer incidence. Nevertheless, we believe that preventive endocrine therapy is suitable in women who are at high risk of developing breast cancer and have no contra-indication to tamoxifen. Medication related side effects should be communicated with prospective high-risk women to encourage adherence and expectation of side effects.

Author's contribution

MJH and IS analysed, interpreted the data, and wrote the manuscript. All other authors read and approved the final manuscript.

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Declaration of competing interest

JC has received research grants from AstraZeneca, all other authors declare no conflict of interest.

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