

## Introduction

- Previous comparisons of tamoxifen vs placebo for breast cancer risk reduction suggest tamoxifen reduces risk in under half of women. Measures to predict who benefits would be useful.
- In the IBIS-I trial, only those women with a  $\geq 10\%$  reduction in mammographic density in response to tamoxifen experienced a reduction in breast cancer risk but this was significant (63%).<sup>1</sup>
- Estimation of density change depended upon a highly trained radiologist
- In this study we explore the value of other approaches to prediction of change using the IBIS-I data as a baseline

## Objectives

The aims of this study were to assess:

- IBIS-I reproducibility
- other measures of mammographic density estimation
- whether blood measures predict density change

## Methods

**Eligibility:** premenopausal women aged 33-46 attending a family history clinic and monitored according to NICE guidelines;  $>17\%$  lifetime risk of breast cancer

**Treatment:** 1 year of treatment with tamoxifen

**Mammographic density:**

- Assessed visually at baseline and year 1 by:
  - IBIS-I reader (RW) who estimated percent density to the nearest 5% and read mammograms independently
  - 2/3 consultant radiologists or advanced radiographic practitioners who marked percent density on a Visual Analogue Scale (VAS) and read baseline and year 1 mammograms at the same time
- A computer thresholding technique (CUMULUS)<sup>2</sup>
- Automated volumetric methods: Quantra<sup>TM</sup> 3 and Volpara<sup>TM</sup> 4

**Other measures:** Lipids, IGF1, insulin and SNPs in the oestrogen receptor and tamoxifen metabolising enzymes

## Results

- 136 of 1279 (10.6%) of eligible women approached wished to enter the study and take tamoxifen. Of these 31 (22.8%) withdrew during the year leaving 105 in the study (Table 1).

Table 1: demographic details

		n	(%)
Parity	Parous	83	(79)
	Nulliparous	22	(21)
BMI	$\leq 23$	35	(33)
	24-25	13	(12)
	26-29	30	(29)
	$\geq 30$	26	(25)
BC Risk (%)	17-29	26	(25)
	$\geq 30$	79	(75)
Age (median)		42.4	

- Of those that had their weight recorded during the study (n=104) 12 (11.5%) had  $>3\%$  weight gain, 29 (27.9%) had  $>3\%$  weight loss and 63 (60.6%) remained stable.

Table 2: Area based measures (percent density)

% point change*	RW IBIS-I# (242)	RW (105)	VAS (105)	Cumulus (98)
40+	2 (1)	0 (0)	0 (0)	1 (1)
30+	14 (6)	5 (5)	0 (0)	3 (3)
20+	34 (14)	12 (11)	0 (0)	13 (13)
10+	91 (38)	35 (33)	6 (6)	30 (31)
0+	97 (40)	49 (47)	81 (77)	43 (44)
increase	4 (2)	4 (4)	18 (17)	8 (8)

\*percentage point change e.g. change from 40% to 30% would be a 10% change  
# change in pre-menopausal women

- Table 2 shows good reproducibility between pre-menopausal women in IBIS-I and the current study (RW and Cumulus). However in-house radiologists saw less reduction.

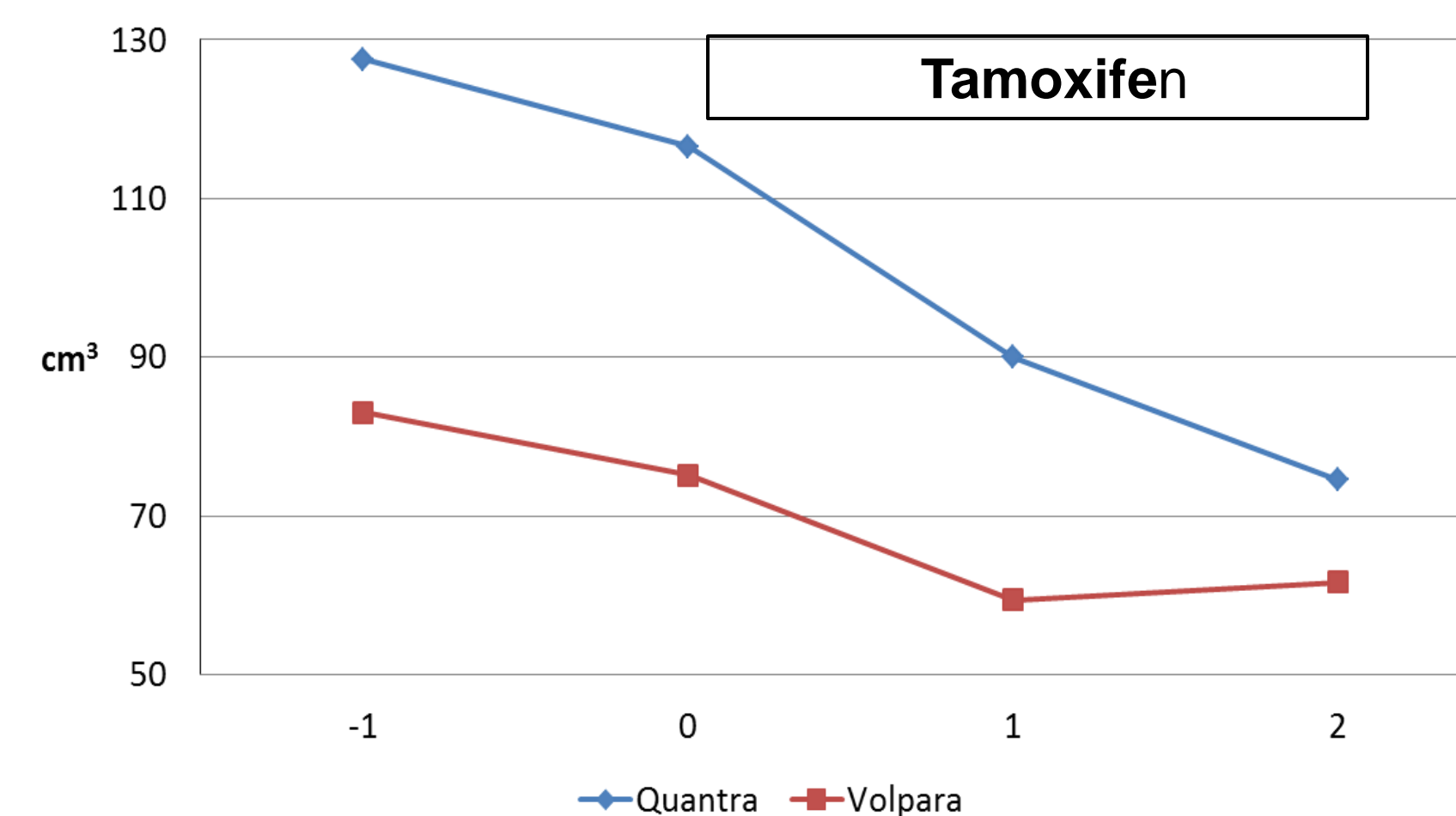
Table 3: Volumetric based measures (Volpara<sup>TM</sup> and Quantra<sup>TM</sup>)

n	% point density change*		% reduction in dense volume#			
	Volpara <sup>TM</sup> (98)	Quantra <sup>TM</sup> (98)	Volpara <sup>TM</sup> (98)	Quantra <sup>TM</sup> (98)	Volpara <sup>TM</sup> (98)	Quantra <sup>TM</sup> (98)
40+	0 (0)	0 (0)	5 (5)	15 (15)	15 (15)	15 (15)
30+	0 (0)	0 (0)	15 (15)	14 (14)	14 (14)	14 (14)
20+	0 (0)	1 (1)	24 (24)	20 (20)	20 (20)	20 (20)
10+	0 (0)	9 (9)	26 (27)	17 (17)	17 (17)	17 (17)
0+	71 (72)	63 (64)	11 (11)	16 (16)	16 (16)	16 (16)
increase	27 (28)	25 (26)	17 (17)	16 (16)	16 (16)	16 (16)

\* Change from baseline to year 1 as a proportion of baseline  
# Change from baseline to year 1 as a proportion of baseline

- Table 3 shows little change in volumetric percent density methods, whereas a greater than 10% reduction in dense volume was seen in 68% of women for Quantra<sup>TM</sup> and in 72% for Volpara<sup>TM</sup>.

Figure 1: Change in dense volume (cm<sup>3</sup>) over time



- Figure 1 shows the change in dense area from the year prior to study entry until year 2 for women who continued medication after one year and for whom data was available (n=51).

Table 4: Change in triglycerides, IGF1 and insulin in women with  $\geq 10\%$  v  $<10\%$  percentage visual density change (RW)

	Baseline		Year 1			
	n	Mean	SD	Mean		SD
<b>&lt; 10%</b>						
Triglycerides	53	1.11	0.56	1.42	0.89	<b>0.000</b>
IgF1	53	157.32	55.26	122.21	38.54	<b>0.000</b>
Insulin	52	55.48	32.84	67.37	55.64	0.102
<b><math>\geq 10\%</math></b>						
Triglycerides	52	0.998	0.54	1.06	0.49	0.127
IgF1	52	163.1	43.99	132.94	32.58	<b>0.000</b>
Insulin	52	43.72	18.16	52.32	25.1	<b>0.003</b>

- Table 4 shows triglycerides were significantly increased in low density change ( $p < 0.001$ ). No other markers were useful.

## Conclusions

1. Density reduction was reproducible between studies (RW)
2. Detection of change difficult in general radiological practice
3. Absolute measures of dense area and dense volume show greatest changes and may be most useful for clinical practice, however their relationship with the long-term effect of tamoxifen and the prevention of breast cancer needs to be established
4. Serum triglycerides may be a surrogate marker of density change.

## References

1. Cuzick J, Warwick J, Pinney E, Duffy SW, Cawthron S, Howell A, Forbes JF, Warren RW. (2011) Tamoxifen-Induced Reduction in Mammographic Density and Breast Cancer Risk Reduction: A Nested Case-Control Study. *J Natl Cancer Inst*; 103(9):744-752.
2. Byng JW, Boyd NF, Fishell E, Jong RA, Yaffe MJ. (1994) The quantitative analysis of mammographic densities. *Phys. Med. Biol*; 39(10):1629.
3. Hartman K, Highnam R, Warren R, Jackson V. (2008) Volumetric Assessment of Breast Tissue Composition from FFDM Images. *Proceedings of the 9th International Workshop on Digital Mammography (IWDM 2008)*; 5116: 33-39.
4. Highnam R, Brady M, Yaffe M, Karssemeijer N, Harvey J. (2010) Robust Breast Composition Measurement - Volpara<sup>TM</sup>. *Proceedings of the 10th International Workshop on Digital Mammography (IWDM 2010)*; 342-349.

QR  
Code