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► **To cite this version:**

D Gareth Evans, Michelle Harvie, Nigel Bundred, Anthony Howell. Uptake of breast cancer prevention and screening trials. *Journal of Medical Genetics*, 2010, 47 (12), pp.853. 10.1136/jmg.2010.082768 . hal-00579026

HAL Id: hal-00579026

<https://hal.science/hal-00579026>

Submitted on 23 Mar 2011

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Uptake of breast cancer prevention and screening trials

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Abstract 151 words

Background: Uptake of cancer trials and in particular prevention trials has been disappointing globally.

Methods: We have assessed uptake to three randomized chemotherapy breast cancer prevention trials and two dietary prevention trials in women at increased familial risk and compared it with uptake of screening trials across a range of risk categories.

Results: Uptake of drug prevention trials remains low at 5.3-13.6%, but is significantly higher in the high (12%) compared to very high risk group (8.4%) for IBIS1 and IBIS2 combined ($p=0.004$). Recruitment to two dietary prevention studies via mailshot was also disappointingly low at 6.2% and 12.5%. In contrast uptake to two mammography screening trials was >90% in all risk categories.

Conclusions: More work must be done to improve recruitment to prevention trials if they are to be seen as viable alternatives to risk reducing surgery.

Impact: Trial designs and decision aids need to be developed to improve recruitment.

1323 words

Introduction

Recently breast cancer (BC) trials' uptake has improved. In 2008/2009 14,359 BC patients were recruited to UK trials representing 33% of incident cases, with 9.1% joining randomized trials[1]. For the same year 93/428 (22%) BC patients at our institution entered randomized treatment trials and 70 of 248 (28%) over a more limited time span entered into a randomised study comparing three different diet/exercise programmes after surgery. This represents uptakes of 47%/45% of eligible patients. Prevention trials can improve the statistical power of their studies by recruiting individuals with a higher risk of the specific cancer. Indeed this might be expected to improve recruitment as people at higher risk of a cancer may be more motivated to join a trial. We previously reported a relatively low uptake of the double blind tamoxifen versus placebo trial IBIS1 amongst women very high risk of breast cancer (lifetime risk 40%+)[2]. We have here enlarged this study to investigate uptake across a range of risks to a number of breast cancer prevention studies.

Patients and Methods

The Manchester Breast cancer Family History Clinic has now seen and assessed over 9000 women since 1987. Lifetime risks of breast cancer are calculated using a manual lifetables approach and using the Tyrer-Cuzick model[3]. Records are kept of all women approached for prevention studies. We assessed the proportion of women who opted for three chemoprevention studies; two placebo controlled studies of tamoxifen (IBIS1) and

anastrozole (IBIS2) and a randomized study using a combination of raloxifene and zoladex (RAZOR) vs. placebo as well as two dietary intervention studies; a non randomised trial to assess the effect of weight loss on markers of breast cancer risk over 12 months (Lifestyle Study) (n=40)[4] and a randomised study comparing two different weight loss diets over 6 months (Intermittent diet study (n=54)[5]. Uptake to these trials was compared across lifetime breast cancer risk categories to two screening trials (FH01/FH02) of mammography aged 40-45 and 35-39 years respectively (Table 1). Lifetime risk categories were: very high risk women (lifetime risk 40%+); high risk (lifetime risk 26-39%) and moderate risk (lifetime risk 17-25%). Women were only counted as being approached if eligible. Women who had previously undertaken risk reducing mastectomy were excluded.

The drug and screening trials report the numbers of eligible subjects personally invited to the study by clinical staff within the Family History Clinic.

Recruitment to the weight loss studies involved a mail shot.

Results

In total 861 very high risk women (lifetime risk 40%+), 1713 high risk women (lifetime risk 26-39%) and 1785 women at moderate risk (lifetime risk 17-25%) were approached for at least one drug or diet trial. Uptake to drug trials was 5.3–13.6%. Uptake to the IBIS1 study was higher amongst high but not very high risk group. This was less evident for IBIS2, but the combined assessment showed a significant difference in uptake 12% vs 8.4% ($p=0.004$). RAZOR was initially targeted only at the very high risk group of 601 women. The recruitment rate was only 5.5% and therefore had to be opened out to the other risk categories. Complete records of high/moderate risk women approached were

not available, but uptake was estimated to be higher: 11% high risk and 8% for moderate risk women. In contrast 699/737 (95%) and 372/401 (93%) women eligible for the screening trials (FHO1/FH02) were recruited with only 6 women returning their consent forms or stating in clinic saying they declined entry.

The lower uptake rate for dietary studies reflects the general poor response to mail shots. Only 12.5% (40/340) entered the lifestyle study and 6.2% (50/797) entered the intermittent study. There was no consistent pattern of uptake to these studies according to risk categories. This most likely reflects that motivation to join a weight loss study reflects a general desire to lose weight and is not motivated by risk reduction.

Uptake to drug prevention studies thus remains low. In the highest risk group of unaffected *BRCA1/2* mutations carriers only 22/256 (8%) have entered a prevention trial, whereas risk reducing surgery uptake was >50% after 7 years[6]. This also compared to 319/1713(18.6%) high risk (p=0.001) entering a prevention trial.

Discussion

We have shown that uptake to drug prevention trials remains disappointingly low at 5.3-13.6%. In contrast the great majority of women from all three risk categories have entered a non randomized screening trial. Uptake of screening is already known to be much higher than of prevention studies with the majority of highest risk women entering MRI screening [2]. The reasons for the poor uptake to prevention trials need to be explored. Anecdotally our high risk women report not feeling comfortable with placebo studies as they will wish to be in an active treatment arm. It is likely that trials aimed at this very high risk group will need to consider dropping a placebo arm in favour of two

proven preventive agents before recruitment is likely to rise. For entry into the STAR trial which involved randomization to either tamoxifen or raloxifene, but did not have a placebo, uptake was higher. A total of 184,460 women were screened using the modified Gail model to determine their breast cancer risk. Of these, 96,368 had a 5-year risk of at least 1.66% [7]. From this group, 20 616 (21.4%) agreed to be screened to determine full eligibility for the trial based on the medical criteria defined below; 20,168 were found to meet all eligibility criteria of the study. Of this latter group, 19,747 women expressed a desire to go forward with participation in the trial, signed a consent form, and were randomized to receive either tamoxifen or raloxifene. Participants were screened and enrolled through nearly 200 clinical centers throughout North America. This multicentre trial represents an adjusted uptake of 21%.

It is certainly possible that women at very high risk do not feel that the potential risk reductions of 35-70% are sufficient given their high absolute risk of breast cancer. Recent introduction of MRI screening in the UK might have improved uptake of prevention studies with the possibility of reliable early detection. However, if anything uptake of prevention trials appears to have reduced in more recent cohorts and uptake of risk reducing mastectomy has not dropped [4]. Perhaps this is linked to widespread press coverage of adverse effects of certain cancer prevention drugs [8] and hormone treatments [9]. Improving risk communication may have some benefit in uptake according to research on uptake of screening [10].

Recruitment to clinical trials is likely dependant on a number of factors such as having a dedicated trial manager, being a cancer or drug trial, and having interventions only

available inside the trial [11]. Training of study staff has also been highlighted as an important area [11-13], and providing them with a best practices tool box that in the future would include successful mechanisms for eligibility screening and recruitment [12]. Development of complex interventions to target poorly recruiting centres or individuals that include training has also shown some success [13].

We are not aware of any other groups that have assessed uptake across a series of prevention trials, or to specify this by risk category. Uptake of tamoxifen in North America where it is licensed for prevention (this is not the case in Europe) has shown only 0.2% of the female population aged 40-79 taking the drug in the year 2000 [14]. However, this study was not able to assess uptake in those strictly eligible on risk grounds or after being approached with prevention as an option. Amongst *BRCA1/2* mutation carriers a Canadian group reported 11% uptake (29/270) of either tamoxifen or raloxifene in women who had not undergone risk reducing mastectomy [15]. This figure is rather similar to our 8% uptake in mutation carriers for any drug prevention trial. It is likely that more must be done before we will get sufficient individuals into cancer prevention trials to move forward on an alternative to surgery in the highest risk groups.

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Competing interest: None to declare

Acknowledgments: We acknowledge the support of the Biomedical Research Centre at

Central Manchester Foundation Trust, NIHR and the Genesis Breast Cancer Prevention
Appeal.

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Table 1: Uptake to prevention and screening trials in the Family History Clinic based on lifetime risk

Date of study recruitment	Study	Method of approach	Number approached	Proportion of approached recruited by breast cancer risk categories		
				40%+ Very High	26-39% High	17-25% Moderate
Drug trials						
1993-2000	IBIS1	Face to face	2278	32/346 (9%)	179/1316 (13.6%)	62/616 (10%)
2002-2005	RAZOR	Face to face		32/601 (5.3%)	33 ^{\$} (11%)	5 ^{\$} (8%)
2003-present	IBIS2	Face to face	1264	14/201 (7%)	55/645 (8.5%)	34/418 (8%)
Screening study						
2002-2007	FH01	Face to face	737	156/167 (93%)	350/371 (94%)	193/199 (97%)
2006-present	FH02	Face to face	503	92/98 (94%)	176/188 (94%)	104/115 (90%)
Diet studies						
2002	Lifestyle Study * +	Mailshot	320	---	5/14 (35%)	35/306 (11%)
2006-2008	Intermittent diet study *	Mailshot	797	7/38 (18%)	24/392 (6%)	19/367 (5%)
IBIS1+2		Face to face	3542	46/547 (8.4%)	234/1961 (12%)	96/1034 (9.3%)
P value V high/high				Chi sq 8.13 P=0.004		
P value High/mod						Chi sq 4.84 P=0.028

*Patients invited to study by mail shot

+ The Lifestyle study only approached women at moderate and high risk

\$ -Estimated uptake: Complete records of high and moderate risk women approached were not available.