results were confined to a small sample from which it is not possible to draw firm conclusions. Such preliminary results, however, suggest that the circulating levels of oestrogen in prolonged OC users do not result in the induction of raised levels of ER message nor does the latter appear to be the case in abnormal TZ compared with internal control tissue. The method of mRNA extraction may prove valuable for the detection of high molecular weight messages in other tissues refractile to extraction and ER message in other human tumours, as well as being a prototype study for ER message levels in cervix tissues.

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Interval Cancers and Sensitivity in the Screening Centres of the UK Trial of Early Detection of Breast Cancer

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The incidence rates of interval cancers following a negative breast screen in two screening centres which offered women aged 45–64 annual screening by mammography and/or clinical examination are examined. Sensitivity of screening is estimated by comparing the incidence rate of interval cancers with that expected in the absence of screening, and the results are compared with those from alternative methods of calculating sensitivity. The incidence rate of cancers diagnosed within 12 months of a negative screen by mammography plus clinical examination was reduced by 70% for women aged 45–54, and 84% for women aged 55+. There is no indication from this that sensitivity in the UK trial was substantially lower than in other studies which have achieved larger reductions in mortality.
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INTRODUCTION

A LARGE MULTICENTRE trial to assess the effect on mortality from breast cancer of screening by mammography and clinical examination, was started in the UK in 1979 [1]. After 10 years, an analysis of mortality showed a reduction in deaths from breast cancer of 20% in the two screening centres combined compared with four comparison centres ($P = 0.01$).

The rate at which new breast cancers appear following a negative screen is an important indicator of the sensitivity of the screening test, which will affect the potential benefit of screening. The increase in the rate of such interval cancers with time following a negative test also provides information on the natural history of the disease, and on the intervals at which screening should be performed to optimise the benefit:cost ratio. This paper gives information on interval cancers diagnosed in the two screening centres within the trial.

PATIENTS AND METHODS

A detailed account of the method of the trial is given elsewhere [1]. The two screening districts, Edinburgh and Guildford, invited the initial cohort of women to screening over a 2–3 year period. In Guildford all women aged 45–64 registered with a general practitioner in the district were invited to be screened. In Edinburgh, the population offered screening consisted of women aged 45–64 registered with a randomly selected half of general practices; the other half formed a control group for a parallel trial and are not included in this analysis. In both centres, women were re-invited at 12-month intervals for a total of seven screening rounds; routine screening was by mammography and clinical examination in rounds 1, 3, 5 and 7, and by clinical examination only in rounds 2, 4 and 6. In Guildford, women failing to attend in round 1 were re-invited in year 3, and the non-attenders were invited again in years 5 and 7; in Edinburgh, only those attending in round 1 were re-invited.

In Guildford, 294 women, including 12 in whom breast cancer was diagnosed, attended for screening before their date of invitation and have been excluded from the trial population.

The trial also included four comparison centres, in which no intervention took place, but in which all women aged 45–64 were identified and followed in the same way as in the screening districts.

The entire populations have been flagged at the National Health Service Central Registers which provide routine information to the trial on all subsequent cancers registered, and all deaths, in the trial population. Information on breast cancers not diagnosed at screening was obtained both through the flagging system and from local searching of pathology laboratory records.

The description of interval cancers is complicated by the different modalities of screening at different rounds, and by the fact that not all women followed the protocol exactly. In particular, some were screened by mammography at the clinical examination only rounds because of problems at the previous screen, whilst some women failed to attend for the clinical only screening rounds.

The present analysis is in terms of the modality of screening which a woman actually had at a given screening round, regardless of what was due at that round. An interval cancer is defined as a cancer in a woman with a previous negative screen, who presents either completely outside the screening system, or who returns to the screening clinic because of symptoms. Cases detected at non-routine visits recommended as the result of the previous routine screen are counted as screen-detected and not as interval cases.

The proportional incidence method of estimating the sensitivity of screening is to compare the interval cancers in a given time period with the number of cancers which would have been expected to occur if no screening had taken place [3]. This expected rate (r_a) in women attending for screening has been calculated using the diagnosis rate (r_c) in the four comparison centres combined, but adjusted using the rate (r_n) in the non-attenders in each screening centre to allow for possible selection bias. Thus,

$$r_a = [r_c - (1 - p)r_n]/p,$$

where p = attendance rate. (This adjustment has been done separately for each screening centre and for the three age groups at entry 45–49, 50–54 and 55+.) This expected rate has been applied to the number of woman-years in each centre and age group to give the expected number of breast cancers. Subtraction of the observed number of interval cases from the expected number gives the number of cases detected by screening which would otherwise have occurred in this interval. This is then expressed as a percentage of the expected, to give an estimate of the sensitivity of the screening test.

A traditional method of estimating sensitivity has been to take the number of cancers occurring in the 12-month interval following a negative screen as a percentage of the cases detected by the screen plus the interval cases, i.e. assuming that all the interval cases were false negatives at screening, and that all such false negatives would have presented within this interval [4].

A third approach is to estimate the relative sensitivity of clinical examination and mammography in detecting cancers picked up at screens where both examinations were carried out. This has been done using the first clinical and radiological opinion recorded in each case since later opinions were made with knowledge of other findings. Cases detected at non-routine visits are classified according to the findings at the routine screen.

RESULTS

Table 1 shows the number of screen-detected cancers in the two centres combined, according to screening round and modality of screening. Not all women followed the intended screening schedule exactly, for example, nine cancers were found in women attending for the first time in round two, and hence had their first mammographic screen at this round, whilst others had mammography at these rounds because of recommendations from a previous screen.

Table 2 shows the observed interval cases and expected number of breast cancer cases occurring in the time period 0–11 months following a negative mammographic plus clinical screen, i.e. one for which the outcome was to return the woman to routine recall.

The age groups at entry of 45–49 and 50–54 have been combined, since the numbers in each are fairly small and there is no marked difference between them. The estimated sensitivity is slightly higher in Edinburgh than in Guildford in the older age group, and overall the estimated sensitivity is higher in the older age group (83%) than in the younger group (72%), although the difference between the two age groups is not significant ($\chi^2 = 3.72, P = 0.054$).

The number of women failing to attend for a clinical only screen, and thus contributing to the 12–23-month interval was too small to allow meaningful analysis.

Table 3 looks at the interval cancers following a first mammographic plus clinical screen separately from later mammographic screens; the estimated sensitivity of the first screen is lower in both time intervals, but the difference between the two is not significant.

Table 4 shows the interval cancers observed and expected in the 12 months following a clinical only screen. The estimated

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Table 1. Cancers detected by screening round and screening modality

Screening round	Screening modality: 1st mammograph E	G	Total	Subsequent mammograph E	G	Total	Clinical only E	G	Total	Total E	G	Total
1	77	78	155	—	—	—	—	—	—	77	78	155
2,4,6	8	1	9	8	8	16	36	36	72	52	45	97
3,5,7	4	10	14	100	138	238	—	2	2	104	150	254
Total	89	89	178	108	146	254	36	38	74	233	273	506

Mammographic screening rounds included a clinical examination. E, Edinburgh; G, Guildford.

Table 2. Interval cancers following any mammograhpic screen

		Observed	0–11 months Expected	Women-years	Detected (%)
Age 45–54 at entry	Edinburgh	12	43.8	24747	73
	Guildford	14	47.6	29727	71
	Total	26	91.4	54474	72
Age 55–64 at entry	Edinburgh	4	38.4	20774	90
	Guildford	10	45.5	23559	78
	Total	14	83.9	44333	83
All ages	Edinburgh	16	82.2	45521	81
	Guildford	24	93.1	53286	74
	Total	40	175.3	98807	77

Table 3. Interval cancers following a first or subsequent mammographic plus clinical screen

	Observed	0–11 months Expected	Women-years	Detected (%)
1st screen	15	55.7	31413	73
Subsequent screens	25	119.6	67394	79

sensitivity for all ages is 66%, with no significant difference between the two age groups.

The percentage of interval cases less than 2 cm in diameter is 63% in Guildford and 50% in Edinburgh for cases occurring within 12 months of a negative mammographic plus clinical screen. This compares with 36% for all cancers in the comparison

Table 4. Interval cancers following a clinical screen

	Observed	0–11 months Expected	Women-years	Detected (%)
Age 45–54 at entry	23	62.4	37365	63
Age 55–64 at entry	18	58.3	30659	69
All ages	41	120.7	68024	66

centres; the figures are similar for cases following a first or subsequent screen.

Using the traditional method of calculation, the sensitivity of mammography plus clinical for Edinburgh and Guildford is estimated at 92% (197/213) and 91% (235/259), respectively. The sensitivity of the first screen is estimated as 92% (178/193), and subsequent mammographic screens as 91% (254/279). The sensitivity of the clinical only screen is estimated as 64% (74/115).

Table 5 gives the results of calculating relative sensitivities for Guildford for first and subsequent screens. Taking both "localised benign" and "suspicious" to indicate detection, the relative sensitivity of mammography is 93% (83/89) for the first screen and 90% (132/146) in subsequent screens. The sensitivity of clinical examination is 72% (64/89) at the first screen and 42% (61/146) at later rounds.

Table 6 gives the same data for Edinburgh. The relative sensitivity for mammography is 94% (84/89) for the first screen and 92% (99/108) for later screens, whilst the figures for clinical examination are 67% (60/89) and 47% (51/108), respectively.

DISCUSSION

Since the reduction in breast cancer mortality observed in the UK trial was lower than that found in some other studies, it is of interest to consider to what extent this difference may have been due to lower sensitivity of screening.

Considering only the 12-month interval following a negative screen which included mammography, the percentage of cases detected by screening can be estimated for the HIP study as 76% [4]. For the Swedish two counties study the figure is 82% [5]. Neither of these estimates is adjusted for possible

Table 5. Method of detection of cancers—Guildford

Radiological opinion	Clinical opinion: None/diffuse	Localised benign	Suspicious	Total
1st screen				
Normal/dysplasia	2	4		6
Localised benign	7	5	—	12
Suspicious	16	15	40	71
Total	25	24	40	89
Subsequent screens				
Normal/dysplasia	4	10	—	14
Localised benign	32	10	—	42
Suspicious	49	19	22	90
Total	85	39	22	146

Table 6. Method of detection of cancers—Edinburgh

Radiological opinion	Clinical opinion None/diffuse	Localised benign	Suspicious	Total
1st screen				
Normal/dysplasia	—	1	3	4
Localised benign	5	1	2	8
Suspicious	24	9	44	77
Total	29	11	49	89
Subsequent screens				
Normal/dysplasia	3	4	2	9
Localised benign	4	1	7	12
Suspicious	50	5	32	87
Total	57	10	41	108

selection bias; in fact, this adjustment works in different directions in the different age groups and makes little difference to the overall estimate of sensitivity; the equivalent unadjusted figure for the UK trial is 76%. However, it should be borne in mind that due to the non-randomised design of the UK trial, the breast cancer incidence rate in the comparison centres may not be an accurate indicator of the underlying rate in the screening centres. Nevertheless, there is no indication that sensitivity is substantially lower in the UK trial.

The proportional incidence method of expressing sensitivity gives a better estimate for a first screen than for subsequent screens, since for subsequent screens some of the expected cases apparently detected may, in fact, have been picked up by an earlier screen, which would result in an over-estimate of sensitivity. There is also a belief that the quality of mammography in both centres improved during the course of the trial, and there is a suggestion from Table 3 that sensitivity improved after the first screening round, although the difference was not statistically significant.

The estimate of sensitivity following a clinical only screen (Table 4) is similarly complicated by the fact that some of the expected cancers will have been picked up by the previous mammographic screen. Thus 66% is likely to be an overestimate of the sensitivity of the clinical screen. Alternatively, the cases detected at clinical only screen can be added to the interval cases in the second year following a negative mammographic plus clinical screen; this gives a 2-year estimate of the sensitivity of mammography plus clinical of 45%. However, this will be an underestimate, since not all the cases detected at clinical screens would necessarily have otherwise presented as interval cases during the ensuing year.

Tables 5 and 6 suggest that overall 8% of cancers detected at screens which included both mammography and clinical examination would not have been detected by mammography alone. This compares with 45% for the HIP study [3]. Whilst an improvement in the sensitivity of mammography has undoubtedly taken place since the HIP study was carried out, those cases missed which would have presented within 12 months following a negative mammographic screen, are probably those most likely to have been detected by clinical examination. Hence the sensitivity of mammography alone, estimated by the proportional incidence method, could be considerably lower than that for the combined mammographic and clinical screens used in this trial. The annual screening protocol of the UK trial makes it difficult to draw any conclusions on the sensitivity of screening in detecting cases with a lead-time of more than 12 months, and it may be the detection of these cases which increases the effect on mortality.

This paper demonstrates the difficulty of estimating the true sensitivity of screening, particularly for screening rounds after the initial one. All the various approaches will be inaccurate; the proportional incidence method will overestimate the sensitivity of later screening rounds, whilst the traditional method will overestimate the sensitivity of all screening rounds since many of those cases detected by screening would not have presented in the subsequent 12 months time interval. The alternative is to adopt a modelling approach, which in turn requires some assumptions concerning the natural history of the disease.

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