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Early discharge of low-risk women from cervical screening

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Abstract

Background

The Scottish Cervical Screening Programme currently offers three-yearly screening to all women between the ages of 20 and 60. However, previous studies have indicated that well-screened women over the age of 50 are likely to be at low risk of cervical neoplasia. This study aimed to explore the implications of discharging these women from screening in a typical area of Scotland.

Methods

1. Case-control study of the screening histories of women with and without screen-detected cervical neoplasia between ages 50 and 59 in Lanarkshire.
2. Cross-sectional study of the prevalence of adequate screening histories among women currently aged 50 in Lanarkshire.
3. Use of routine screening programme statistics to estimate the effects of introducing an early discharge policy.

Results

1. Women reaching the age of 50 with two recent, consecutive, negative smears had reduced odds of screen-detected neoplasia in the subsequent decade.
2. The estimated odds ratio for all screen-detected neoplasia (CIN 1-3, adenocarcinoma in situ and invasive carcinoma) was 4.4 (95% confidence interval 1.6-13.2, $p=0.002$).
3. The estimated odds ratio for screen-detected high-grade CIN and invasive squamous carcinoma was 17.0 (95% confidence interval 2.4-243.0, $p=0.0004$).
4. 54.0% (95% confidence interval 47.9%-59.9%) of screening participants currently aged 50 fulfilled the definition of adequate screening.
5. Discharging these women might be expected to reduce screening workload by approximately 10%, but those discharged would be at increased risk of neoplasia.

Conclusion

Now that full screening histories are available in all health board areas since 1990, the identification of a low-risk group within the screened population could be the first step towards a screening programme targeted more closely on those with the greatest capacity to benefit.

Introduction

The Scottish Cervical Screening Programme currently offers cervical screening to all women aged between 20 and 60 at three-yearly intervals. Cervical cancer incidence and mortality have fallen since the introduction of the programme, but some have argued that this has been achieved at the expense of investigating and treating large numbers of women needlessly. In other words, the programme has achieved high sensitivity at the cost of low specificity. [1] This arises partly from an inability to distinguish lesions which may regress from those which will progress to malignancy, and partly from the practice of offering screening to all women in the specified age range, irrespective of their underlying risk of disease.

The 1997 Guidelines for clinical practice and programme management therefore recommended that consideration be given to identifying low-risk women and discharging them from screening. This would be expected to benefit the women, who would avoid several smear tests, and to improve the efficiency of the programme. [1]

In an area with an established screening programme, there will be a group of older women who have accumulated a series of negative cervical smears. These well-screened women are unlikely to have cervical intraepithelial neoplasia (CIN), a precursor of invasive cancer, which is in any case commoner in younger women. [2] Older women may also be less likely to harbour cervical infection with high-risk types of the human papillomavirus (HPV), an important determinant of cervical neoplasia, and less likely to be exposed to the virus through multiple sexual partners. [3,4,5]

Case-analysis studies in Tayside and Grampian have found that few of the women developing cervical neoplasia after the age of 50 have been adequately screened prior to age 50. The authors of these studies have therefore suggested that adequately-screened women might be discharged from screening from the age of 50. [6,7,8,9] In addition, cohort studies in Nordic populations have shown that detection rates for CIN fall with increasing age, and with the number of previous negative smears. In one cohort of 5893 women with three negative smears before 50 and one negative smear after 50, only 9 cases of in situ or invasive cancer occurred in the following decade. [10,11]

Sherlaw-Johnson et al have modelled the effects of reducing the upper age limit for screening in England. The withdrawal of women from age 50 following four consecutive negative smears was predicted to reduce smear test and colposcopy workload substantially, but at the cost of two additional cases of invasive cancer per 100,000 women per year. [12]

The observational studies to date have been performed in areas which were early adopters of population-based screening and centralised record-keeping. Their methods and findings cannot necessarily be generalised. Therefore, this study aimed to investigate the association between screening history and the subsequent risk of screen-detected disease, using routinely-available records in a typical area of Scotland, and to explore the implications of different possible criteria for discharge from screening.

Methods

The research comprised a case-control study and a cross-sectional study, supplemented by an examination of routine screening programme statistics. Approval was granted by the Lanarkshire Ethics of Research Committee.

Case-control study

Subjects

Cases comprised all women with a histopathological diagnosis of cervical intraepithelial neoplasia (CIN) or cervical cancer, made following a smear (index smear) taken between the ages of 50 and 59 and during the period 1995-1999, and processed at Monklands Hospital, the only cervical cytology laboratory in Lanarkshire.

Cases were ascertained from the Pinnacle database at Monklands Hospital, which contains all biopsy results from Monklands, and notifications of biopsies performed at the other colposcopy clinics in Lanarkshire. Cases without an identifiable index smear were assumed to have presented clinically and were excluded from the study. The possibility that some index smears were taken during the investigation of a symptomatic cancer cannot be excluded.

A matched control for each case was obtained by identifying the first negative smear reported on the same, or next, day from a woman of the same age.

Exposure

Each woman's screening history since the age of 40 was categorised according to four alternative definitions of adequate screening, based upon those used in previous published studies (Table 1). [6,8,9] An interval of two to four years between smears was deemed acceptable, to allow for women who may have missed initial appointments or been subject to delays in recall. A screening history was still categorised as adequate if there were additional negative smears between those which met the interval criteria.

Each woman's screening history was initially ascertained from the cytology database. However, computerised cytology records in Lanarkshire are incomplete prior to 1990. Therefore, additional earlier smear results were sought where necessary, first from the call/recall database, and then from the woman's general practitioner (GP).

Cross-sectional study

The call/recall database was searched by date of birth to identify a birth cohort of all women born in January 1950 and currently eligible for screening in Lanarkshire. The screening history for each woman was obtained from her call/recall record, and categorised according to the different definitions of adequacy (Table 1).

Screening programme statistics

The age structures of (i) the population of women eligible for screening in Lanarkshire, and (ii) the population of women screened within the last year in Lanarkshire, were obtained from the routine statistical return ISD(D)4 for the year ending 31 March 2000 (Information Services, Lanarkshire Health Board).

Analysis

The distribution of diagnoses among the cases, and the proportions of cases and controls fulfilling the various definitions of adequate screening, were analysed using Minitab.

A matched case-control analysis was then carried out, using each definition of adequate screening in turn as the exposure variable. For each 2x2 table, the odds ratio was estimated, the null hypothesis of no association was tested using McNemar's continuity-corrected chi-squared (X^2) statistic, and a 95% confidence interval was calculated using the Normal approximation to the Binomial distribution, all using Epi Info.

For one 2x2 table (D) in which the sum of the discordant pairs was less than 10, the 95% confidence interval was calculated using the exact Binomial method. [13]

The dataset was then partitioned to exclude cases of CIN 1, adenocarcinoma in situ and adenocarcinoma. This left cases of high-grade squamous neoplasia (CIN 2, CIN 3 and squamous carcinoma), the most important disease states cervical screening can be expected to detect. A matched case-control analysis of the association of high-grade squamous neoplasia with adequacy definition A was carried out as described above.

95% confidence intervals for the proportions of women with adequate screening histories in the cross-sectional study were calculated using Minitab.

Population attributable risk (PAR) fractions were estimated using the expression

$$PAR = \frac{p(R-1)}{1+p(R-1)}$$

where p represents the estimated population prevalence of inadequate screening from the cross-sectional study, and R , the relative risk, is approximated by the estimated odds ratio from the case-control study. [14]

In order to estimate the potential effects of an early discharge policy on screening workload, it was assumed that the proportion adequately screened in the current 50-year-old cohort could be applied as an average to the entire 50-60 age group.

Results

Case-control study

75 cases and matched controls were identified. The distribution of diagnoses among the cases is shown in Figure 1. CIN 3 accounted for approximately half of the cases; there were few invasive cancers.

Data from the cytology and call/recall databases were sufficient to determine the exposure history for only 43 (29%) women. GPs returned data for 95 (89%) of the remaining 107 women. Overall, complete categorisation of exposure was possible for 64 (85%) of the matched pairs.

The numbers and proportions of cases and controls whose screening histories fulfilled the different definitions of adequacy are shown in Table 2. 13/69 (19%) of cases fulfilled at least one definition of adequate screening. CIN 1 and glandular lesions accounted for 8/13 (62%) of these adequately-screened cases, compared with 18/75 (24%) of cases in total.

The results of the matched analysis of the exposure patterns of case-control pairs for each definition of adequate screening are shown in Table 3.

Cross-sectional study

Of 278 women eligible for screening, 150 had had two consecutive negative smears prior to age 50 (54.0%; 95% confidence interval 47.9%-59.9%). 113 had had three consecutive negative smears (40.6%; 95% confidence interval 34.8%-46.7%).

Table 4 shows the estimated reduction in screening workload associated with the early discharge of women with two, or three, consecutive negative smears.

Calculation of the population attributable risk fractions (Table 5) estimated that 61% of all screen-detected neoplasia, and 88% of screen-detected high-grade squamous neoplasia, in the 50-59 age group was attributable to inadequate screening, as defined as the absence of two consecutive negative smears prior to age 50.

Discussion

Study design

This is the first UK study to use the case-control method to explore the implications of the early withdrawal of adequately-screened women from cervical screening. A retrospective cohort study would have been the design of choice for this study, but this would have depended upon comprehensive centralised screening records, established since the women were aged 40. Such records did not exist in Lanarkshire prior to 1990. A case-control approach was therefore adopted, despite its well-known hazards of bias and confounding. Controls were matched for screening participation in order to minimise selection bias, and any possible response bias was mitigated by the high response rate from GPs. Migration bias, arising from women having had additional smears processed in other laboratories, cannot be discounted, but this is likely to have affected cases and controls equally and only in small numbers.

Implications of findings

Most women with screen-detected cervical neoplasia between the ages of 50 and 59 had not been adequately screened, by any definition, prior to the age of 50. In previous Scottish studies, even smaller proportions of cases had been adequately screened: 0% of Tayside cases had had two negative smears, and 2.7% of Grampian cases had had three negative smears. [6,8]

An estimated 54% of women currently aged 50 in the Lanarkshire screening programme have accumulated two consecutive negative smears; 41% have accumulated three. In Grampian, Cruickshank et al estimated that 83% of women aged 49 and 50 met the criterion of two negative smears [8]. This strengthens the impression that women in an area with a longer history of organised screening, such as Grampian, are much more likely to have acquired an adequate screening history.

For a woman who reaches the age of 50 with two recent consecutive negative smears, the odds of developing screen-detected neoplasia in the next decade are an estimated 4.4 times smaller than the odds for other screening participants of the same age. In the exploratory analysis of the subgroup of high-grade squamous cases, the estimated odds ratio was substantially higher at 17. Although the confidence intervals for these estimates are wide, reflecting the relatively small size of the study, these differences are highly unlikely to have been observed by chance.

The estimated odds ratios for the more stringent definitions of adequate screening (B, C and D) did not differ significantly from unity. This may reflect the unexpectedly small proportions of control women who fulfilled these criteria. A retrospective power calculation showed that the study was under-powered to detect an odds ratio of 4.4 or greater for these exposure variables; adequate testing of the hypothesis for all exposure variables would require a substantially larger study.

Discharging women with two negative smears at age 50 might be expected to reduce the total number of women being screened in Lanarkshire by approximately 4000 (10%) per annum; if three negative smears were required for discharge, the corresponding reduction would be approximately 3000 (7.5%) per annum. These estimates are considerably lower than the anticipated saving of "up to 18% of smear tests" from Tayside. [6]

The population attributable risk calculations, which depend upon necessarily imprecise odds ratio estimates, indicate that an estimated 39% of all cervical neoplasia, and 12% of all high-grade squamous neoplasia, detected by screening women aged 50-59 is not attributable to prior inadequate screening. Adequately-screened women discharged at age 50 would be at increased risk from disease – predominantly CIN 1 and glandular lesions - which is currently being detected by screening them beyond the age of 50. This is in keeping with the predictions of Sherlaw-Johnson et al. [12]

This study has therefore confirmed that adequately-screened women reaching the age of 50 are at substantially reduced risk of screen-detected neoplasia, but the projected benefits to the screening programme of discharging these women are less than those implied by previous studies. This partly reflects the lower proportion of women in Lanarkshire who have been adequately screened, but may also reflect the fact that the women in this study were drawn from a more recent birth cohort. They may therefore have a higher underlying risk of cervical neoplasia than the women studied in Tayside and Grampian.

A new approach to cervical screening?

Cervical screening is currently offered to a large population of women whose need for screening is assumed to be homogeneous. Apart from the follow-up of abnormal results, no account is taken of previous screening history in planning the recall of individual women. Other identified risk factors for cervical cancer play no significant part in the definition of the need for screening.

This study has confirmed that a group of low-risk older women can be identified within the cervical screening target population on the basis of their recorded screening histories. It may be possible to show, in a larger study, that women meeting more stringent criteria are at even lower risk. The identification of this low-risk group is an example of how epidemiological data might be used to inform a different approach to population screening.

A utilitarian approach would redefine target groups for screening, seeking to maximise programme efficiency by targeting screening on women with the greatest capacity to benefit. Many women might welcome the opportunity to be discharged from screening if they understood themselves to be at low risk, but others might jealously guard the peace of mind conferred by “unnecessary” negative results. Further research might explore women’s views on what level of disease risk justifies screening, and attitudes to a possible re-targeting of the programme. Age and screening history are particularly suitable as criteria for targeted screening, as the necessary information is already available in call/recall databases. Additional variables such as HPV status might also be used, in time, to target screening provided suitable estimates of risk were available.

A more radical, empowering alternative would be to use risk data as a starting point for a participative assessment of an individual woman’s need for screening. Such an approach is already recommended, for example, in determining the need for screening for hyperlipidaemia, and would be consistent with the recent report from the National Screening Committee. [15,16] This might appear threatening, not only to professionals, but also to those women who would prefer not to confront the uncertainty associated with screening. Although a participative approach would require additional training and consultation time, these costs might be justified by a reduction in the number of low-yield smears and the benefits of placing cervical screening within a more holistic, empowering reproductive health consultation. Further research might explore the extent to which women wish to be involved in decision-making in cervical screening, how

best to provide the required information, and whether this would promote uptake among high-risk women - or simply suppress uptake among low-risk women.

Acknowledgements

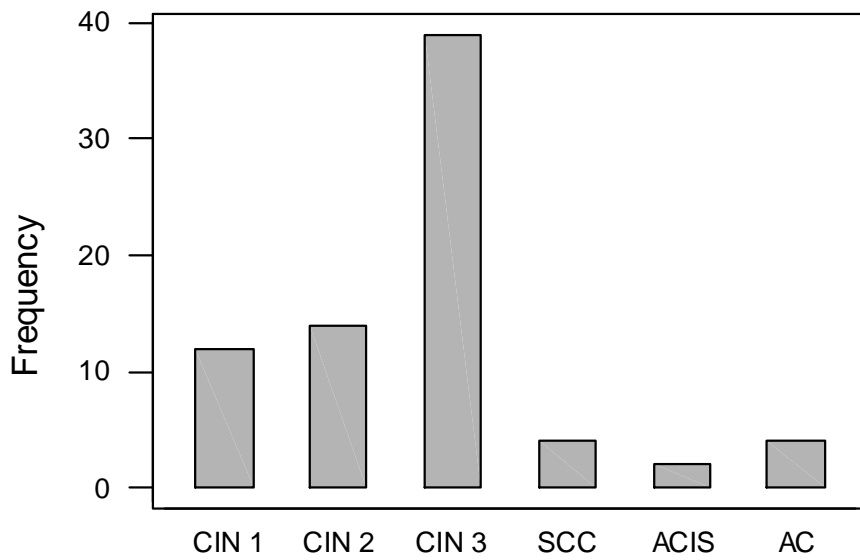
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Table 1 Definitions of adequate screening

Variable	Possible values	Negative smears* before age 50	Negative smears* at or after age 50
A	Yes/No	2	0
B	Yes/No	2	1
C	Yes/No	3	0
D	Yes/No	3	1

*Consecutive negative smears at intervals of between two and four years

Figure 1 Diagnoses of cases



Legend:

CIN cervical intraepithelial neoplasia (grades 1, 2 and 3)
SCC squamous cell carcinoma
ACIS adenocarcinoma in situ
AC adenocarcinoma

Table 2 Proportions of subjects with a history of adequate screening

Definition of adequate screening	Cases fulfilling definition		Controls fulfilling definition	
A	13/69	(19%)	32/70	(46%)
B	7/69	(10%)	7/72	(10%)
C	7/69	(10%)	11/69	(16%)
D	4/69	(6%)	3/72	(4%)

Table 3 Case-control comparisons

Outcome	Exposure	N	OR	95% CI	p
All screen-detected neoplasia, age 50-59	A	65	4.40	1.58-13.23	0.002
	B	67	1.00	0.25-3.96	0.75
	C	64	1.80	0.55-6.15	0.42
	D	67	0.67	0.06-5.82	1
High-grade squamous screen-detected neoplasia, age 50-59	A	48	17.00	2.40-243.02	0.0004

N: number of case-control pairs. OR: estimated odds ratio. 95% CI: 95% confidence interval

Table 4

Estimated effects on screening workload

Screening population denominator	Estimated size of this population (mid-1999)	Estimated number aged 50-60 in this population (mid-1999)	Criterion for discharge	Number (proportion) of 50-60 year olds discharged from screening	Proportion of total denominator population discharged from screening
Women eligible for screening*	154,720	32,767 (21.2% of total)	Two negative smears	17,694 (54.0%)	11.4%
Women screened in the past year†	42,642	7,855 (18.4% of total)	Three negative smears	13,303 (40.6%)	8.6%
			Two negative smears	4,242 (54.0%)	9.9%
			Three negative smears	3,189 (40.6%)	7.5%

*Restricted to women aged 20-60, as the great majority of women over the age of 60 who are eligible for screening have in fact ceased attending.

†Includes women of all ages, as this denominator is a fairer reflection of actual workload than the size of the eligible population.

Table 5

Estimated population attributable risk fractions

Outcome Age 50-59	Exposure Age 40-49	Estimated exposure prevalence from cross- sectional study	Estimated odds ratio from case- control study	Estimated PAR
All screen-detected neoplasia	Absence of two consecutive negative smears	46%	4.4	61%
High-grade squamous neoplasia	Absence of two consecutive negative smears	46%	17.0	88%

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