Risk targeting in cervical screening: a new look at an old problem

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SUMMARY. In the face of continuing debate about the level of effectiveness of the United Kingdom cervical cytology screening programme in preventing cervical cancer, more precise targeting of high risk groups might offer a means of enhancing its efficiency. Broad risk targeting is already practised by screening only sexually active women aged 20 to 65 years. This paper describes a risk scoring system constructed from the available literature and designed to be used by primary care health professionals and patients. The system involves four independent risk factors: educational level, current smoking habit, years of oral contraceptive use and number of sexual partners. Since the objective is simply to identify women at relatively high risk, inclusion of a factor neither requires nor implies causality. The next steps are to study the feasibility of putting the scale to practical use and to investigate its predictive value in a prospective evaluation.

Keywords: cervical screening; morbidity risk factors; screening effectiveness; risk assessment.

Introduction

THE scientific basis of the cervical screening programme in the United Kingdom, the majority of which is carried out in a primary care setting, has once again come under scrutiny[1] in a climate where increasing political pressure in favour of screening in general seems to outweigh concern about its costliness and possible adverse effects.[2,3] While long overdue initiatives aimed at the improved administration of the programme are welcome, there is an absence of controlled trials to establish the efficacy of cervical screening. Although various observational and quasi-experimental studies provide persuasive indirect evidence that cervical screening can reduce morbidity and mortality from cervical cancer,[4] predicted reductions based on this evidence have not been achieved in practice in the UK.[5] This is further complicated by the fact that many of the evaluated programmes have shorter screening intervals than is currently recommended in the UK.[6,7]

Efforts to improve the UK's apparently poor record have understandably concentrated on two areas: biomedical research and the administration of the programme.[8-11] Hopes of identifying the human papillomavirus as a causal organism have been frustrated by evidence of its ubiquitous nature.[12-17] Other research has concentrated on elucidating the natural history of cervical intraepithelial neoplasia with emphasis on distinguishing between the different grades.[18-22] Although there is general agreement that cervical intraepithelial neoplasia is a precancerous stage, particularly the higher grade lesions (CIN2 and CIN3),[23] these issues remain unresolved.

There is one element in the provision of cervical screening programmes which historically has been largely ignored, despite its potential for improving efficiency. This is the question of how to take account of the wide variation in individual risk status for cervical intraepithelial neoplasia. The aim of this paper is to begin to address this omission, by describing the epidemiological basis of a proposed risk scoring system for this outcome.

Risk targeting

The practice of directing the UK cervical screening programme towards all sexually active women in the age group 20–65 years is an example of broad risk targeting. However, risk related intervention is theoretically more efficient than uniform allocation of resources, with the potential benefit increasing with the discriminatory power of the risk score.[24,25]

A number of practical issues remain, including whether it is feasible to measure risk status and whether it is cost effective to use this to influence the delivery of services. Several studies from Finland have in the past made similar attempts to assess the risk targeting approach,[26-28] at a time when there was less epidemiological evidence available regarding independent risk factors. These authors reached pessimistic conclusions about the value of risk targeting in this context, but there are now grounds for considering it once again.

First, by identifying and following a disease free cohort, the study design adopted previously[26,27] sought to identify risk factors for incident rather than prevalent cases. This is not necessarily appropriate since the purpose of the cervical smear test is to detect prevalent asymptomatic disease. Secondly, the risk factors considered by the Finnish authors included signs and symptoms which may be associated with invasive disease. These should be acted upon in their own right and are therefore inappropriate as indicators of asymptomatic cervical intraepithelial neoplasia.

Further, it was argued that the cessation of screening for a group of women at low risk was highly undesirable. However, complete cessation of screening for any group of women is not a necessary consequence of more specific risk targeting, which may for instance be achieved by introducing screening intervals that are graduated according to risk status. Moreover, it has been shown that concentrating all resources on the high risk group is far from optimal unless the detection rate (sensitivity) of the screening test using uniform allocation is extremely low.[24]

Lastly, the Finnish authors claimed that any attempt to use risk related screening intervals presupposes a different natural history of cervical intraepithelial neoplasia in high risk women.[26-28] This does not necessarily follow — all that is presumed is that the incidence of cervical intraepithelial neoplasia will be higher in the high risk group. The objective of risk related schedules is therefore simply to optimize the lead time before development of invasive disease, by differentially

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allocating resources to those women most at risk. Indeed, both the Finnish papers[26,27] and a later comment on risk sensitive screening[28] concluded that concentrating resources on those women at highest risk would be a desirable aim if such women could be successfully identified.

Construction of the risk scoring system

There are a number of ways of deriving risk scoring systems.[29] These range from completely unformalized clinical judgement to a systematic statistical analysis of a large, comprehensive data set. In the absence of the data required for the latter, a third option is to amalgamate the epidemiological information available in the literature to derive a working system which can be assessed for its predictive ability on a new data set.

One problem with utilizing the wide literature on the epidemiology of carcinoma of the cervix and its precursors is that a variety of outcome measures have been considered, as well as many different sets of potential risk factors and study samples. Regarding the outcome measures, it is widely accepted that cervical intraepithelial neoplasia has an invasive potential,[23] and the aetiological features of cervical intraepithelial neoplasia and cancer are therefore thought to be comparable. For the purpose of this study then, the previous studies considered were those with an outcome of either cervical intraepithelial neoplasia or cervical cancer. One possible disadvantage of this approach is that many of these studies include minor degrees of dyskaryosis or cervical dysplasia, which may not have an identical aetiology to cervical intraepithelial neoplasia and cancer.[21,22] This is unlikely to invalidate a scoring system for dysplasia as a practical tool, and indeed a study employing a risk approach may help to shed light on this issue.

The criteria for selecting investigations from the literature were that they should be controlled studies of reasonable size, involving appropriate statistical adjustment for the interrelationships of the potential risk factors. This approach led to five studies being chosen, all reporting results of case control studies using logistic regression techniques to determine independent risk indicators. The outcome measure for three of these studies was cervical dysplasia or carcinoma in situ: 190 cases with 422 controls;[30] 250 cases with 500 controls;[31] up to 206 case–control pairs.[32,33] The outcome for the fourth and fifth studies was invasive carcinoma of the cervix: 178 cases with 855 controls;[34] 418 cases with 704 controls.[35] The Milan study[32,33] also considered invasive cancer as an outcome, but in terms of the results abstracted here the differences between outcomes were negligible.

Risk factors

The first of these suitable studies identified the following four factors as being independently associated with the outcome: years of oral contraceptive use, current smoking habit, number of sexual partners and pregnancy outside marriage.[30] An apparent association with age at first intercourse was found to be entirely accounted for by the number of sexual partners. In contrast, the two Ontario studies[31,34] identified age at first intercourse as a risk factor, but in neither study was 'number of sexual partners' fully taken into account. This criticism does not apply to the Milan study,[33] where age at first intercourse remained significant after controlling for number of sexual partners. On the other hand, the relative risk estimates were much reduced in magnitude after this adjustment, and were ultimately of only marginal statistical significance.

Oral contraceptive use was dismissed in the later Ontario study as secondary to the number of sexual partners;[31] however, this study only compared 'ever used' with 'never used' for oral contraceptive use. Along with others,[36,37] both the Oxford study[30] and the 'US five cities' study[35] demonstrated a notably increased risk only for oral contraceptive use in excess of five to seven years, suggesting that the relationship with outcome would have been considerably underestimated in the Ontario study.[31] Oral contraceptive use among the women in the Milan study has recently been considered,[38] but the numbers were too small for reliable estimates to be obtained.

All five studies identified current smoking habit and number of sexual partners as independent risk factors, with reasonably consistent magnitudes of relative risk. Pregnancy outside marriage was only considered by the Oxford study; in any case this factor would cause problems for a current risk scoring system as a result of the considerable changes in its incidence over time. All three North American studies[31,34,35] identified educational level as an independent risk factor with comparable levels of relative risk. The Oxford study[30] considered social class based on the husband's occupation, but no clear relationship emerged for this factor which is at best an imperfect proxy for the woman's education. The Milan studies[32,33] only considered these factors as potential confounding variables rather than as of interest in their own right.

Other variables, such as parity and income, have been variously observed as risk factors in a minority of these five studies, but as no consistent relationships have been demonstrated they have been excluded from further consideration.

The age of the woman and the interval since her last previous cytology test are both important risk factors for cervical intraepithelial neoplasia, and indeed for cervical cancer.[39,40] In each of the five studies described above the cases and controls were age-matched, and hence any risks derived from the studies can be held to be independent of age. Notwithstanding this, some of the factors considered clearly include an element which is related to age, for example years of oral contraceptive use. In addition, there is the issue of differential risks of the other factors across age groups, that is interactions between, for example, age and number of sexual partners. Generally, this information is not available from age-matched case-control studies (although interactions with age can be investigated they tend not to be reported). In any case, changes in the risk profile by age make it unwise to incorporate this factor explicitly into the core of a risk scoring system.[40]

In conclusion, while the risks suggested by the previous studies are age-independent this does not obviate the necessity to consider age in any prospective independent evaluation of the risk factors suggested by this literature. Similarly, the interval since the preceding smear could, like age, be incorporated fairly easily into a future risk scoring system by utilizing information from family health services authority sources.

Risk scoring system

In summary, four independent risk factors can be chosen from the available literature as best representing the risk of developing cervical intraepithelial neoplasia or cervical cancer: the woman's educational level; current smoking habit; years of oral contraceptive use; and number of sexual partners ever. It must be emphasized that including a risk factor in a scoring system neither requires nor implies causality.[29]

The estimates of independent relative risk attributable to these factors were very similar in the studies considered and those that were reported are shown in Table 1. It should be noted that since all of the original studies were case control studies, these risk estimates should more properly be referred to as odds ratios; for rare conditions the odds ratio may be interpreted as an approximate relative risk.[41] By informally amalgamating the information from these studies, a set of odds ratios for the four factors were obtained (Table 1). More emphasis was placed upon

Table 1. Odds ratios available from the relevant literature, and resultant proposed weightings.

Factor category	Odds ratios found by: Harris *et al*[30]	Clarke *et al*[31]	La Vecchia *et al*[32,33]	Clarke *et al*[34]	Brinton *et al*[35]	Proposed weightings (odds ratios)
Level of education						
College	—[a]	1.0	—	1.0	1.0	1.0
Completed high school at most	—	1.6	—	1.9[b]	2.1[b]	1.6
Current smoking status[c]						
Non-smoker	1.0	1.0	1.0	1.0	1.0	1.0
Smoker:						
<15 per day	2.2	2.9[b]	1.8[b]	2.2	1.5[d]	2.0
15–19 per day	2.5				2.0[d]	
20+ per day	2.1					
Years of oral contraceptive use[e]						
None	1.0	1.0	—	—	1.0	1.0
<5	0.8		—	—	1.2	
5–9	1.8	1.7	—	—	2.5	2.0
10+	2.1		—	—	1.7	
Number of sexual partners[f]						
1	1.0[g]	1.0	1.0	1.0	1.0	1.0
2	2.4	3.4	2.0	1.9	1.5[d]	2.0
3–5	5.4		3.3		2.2[d]	4.0
6+	6.1	6.9				

[a]Harris *et al*[30] did not consider education but did find a significant adjusted odds ratio of 1.6 for 'pregnancy outside marriage'. [b]Unadjusted risks. [c]Very little evidence of dose response either in the categories used here or in the original papers. [d]Unadjusted risks, matching ignored to enable alteration of the reference category. [e]Grouping used by Clarke *et al*[31] would from other studies[30,36,37] be expected to underestimate the strength of the relationship. [f]Clarke *et al*[31] adjusted only for oral contraceptive use; definition used by Clarke *et al*[34] would be expected to 'dilute' the risk. [g]Included five virgins.

odds ratios obtained after more comprehensive adjustment for other factors, such as in the Oxford study.[30] For example, on the question of the choice of categories for number of sexual partners, there seemed little predictive value to be gained by separating the three to five partners category from the six or more partners category, at the cost of increased complexity.

The process of relatively informal pooling of risks is not intended to represent a formal statistical overview or meta-analysis such as those carried out for randomized controlled trials.[42] First, formal methods are not clearly defined for observational studies with such disparate methodologies. Further, the primary objective here is to produce a proposed scoring system which needs to be assessed in terms of predictive value in an independent prospective study; for such a practical risk scoring system where relatively crude weights are required there is therefore little need for exact estimates. In any case, for the risk factors considered, both the slight inconsistencies observed in the available literature and the effects of rounding are well within the margins of error of the original estimates.

In practice, a feasible risk scoring system would require simple additive risks rather than a multiplicative system, hence the inclusion of integral logarithmic scores in Table 2. The range of possible risk scores from 0 to 33 corresponds to an odds ratio of about 26 for the highest risk group compared with the lowest. In order to construct a scoring system that could be applied in practical circumstances, the simplified version shown in the last column of Table 2 has been derived.

Table 2. Weightings of independent risk factors for a proposed risk scoring system for cervical intraepithelial neoplasia among women eligible for cervical screening.

Factor/category	Odds ratio	ln[a] (odds ratio)	ln (odds ratio) x 10, rounded to nearest integer	Simplified version of scoring system
Education				
Higher[b]	1.0	0	0	0
Other	1.6	0.470	5	1
Current smoking status				
Non-smoker	1.0	0	0	0
Smoker	2.0	0.693	7	1
Years of oral contraceptive use				
<5	1.0	0	0	0
5+	2.0	0.693	7	1
Number of sexual partners				
1	1.0	0	0	0
2	2.0	0.693	7	1
3+	4.0	1.386	14	2
Highest possible risk score for an individual			33[c]	5[d]

[a]Natural logarithm. [b]'At least A-level or equivalent' since the proportion of women in this category will be most comparable with that for the education factor in the North American studies.[31,34,35] [c]Scale runs from 0 (odds ratio = 1) to 33 (odds ratio = 25.6). [d]Simplified scale runs from 0 (odds ratio = 1) to 5 (odds ratio = 25.6).

Conclusion

Although all initiatives to improve the administration of the cervical cytology screening programme in the UK are to be welcomed, the concept of risk targeting in cervical screening appears not to have been fully assessed. Most of the arguments against improved risk targeting are not empirical but theoretical with little supporting evidence. Yet risk targeting has been researched and gainfully employed in a number of other areas of medicine.[43-45]

A proposed risk scoring system for cervical intraepithelial neoplasia derived from the literature has been presented here

and thus may be of assistance in risk targeting. There are many questions which remain regarding the use of such a risk scoring 'tool' in practice. For instance, is the application of such a system feasible? Is the collection of such sensitive data acceptable to women? Can such a scoring tool serve an educational purpose and lead to greater autonomy on the part of women participating in the screening programme? The fundamental question of the (positive and negative) predictive value of the scoring system also remains to be resolved.

The questions of the feasibility and acceptability of the risk scoring system — and also that of its reliability — have been addressed in a pilot study. A large prospective study is underway to assess fully the predictive power of the scoring system.

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