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Early withdrawal from cervical cancer screening: the question of cost-effectiveness

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Abstract

In countries such as the UK, mass population screening for cervical cancer has been undertaken since the 1960s. Although of established effectiveness, no formal evaluation of the screening protocol was carried out prior to its implementation. On the basis of a published mathematical modelling exercise, it has been speculated that withdrawing women from the screening programme at an earlier age than at present, whilst leading to a higher rate of invasive cervical cancer (ICC), could reduce resource use. Using estimates of screening and treatment costs, and of expected life-years lost following earlier withdrawal, we simulated cost-effectiveness ratios for various scenarios described by the model. Median cost savings resulting from a life-year lost never exceeded £10 000 for any scenario, although the estimates were particularly sensitive to the assumed age at cancer presentation and the rate of cancer progression. Our findings seem to offer little economic support for the early withdrawal of subjects from the cervical screening programme.

Keywords: Cervical cancer; Cost-effectiveness; Mathematical model; Screening; Simulation

1. Introduction

The natural history of cervical cancer, involving a readily-detectable pre-clinical phase typically lasting for many years, makes the disease especially amenable to screening. The conventional screening technology—the Papanicolaou smear test—is now over 50 years old and screening programmes were introduced in several countries, such as the UK and parts of Scandinavia and of the USA, soon after the test's discovery. Where long-term implementation of screening has been successful, the incidence of invasive cervical cancer (ICC) has fallen [1]. In the USA, non-adherence with regular screening has now been identified as the single most important modifiable risk factor for ICC [2]. In the UK, mass screening was introduced at a local level in the 1960s, although participation rates throughout the following two decades were low and variable. In 1988, the local programmes were re-organised, with a view to enhancing compliance. A national call/re-call system was introduced, as were, 2 years later, incentive payments for those general practitioners who successfully recruited a high proportion of their eligible women (those aged between 20 and 64 years). In consequence, the participation rate in England doubled, from 42% in 1988 to around 85% by the mid-1990s, whilst the annual incidence of ICC fell by more than 35% [3].

Nowadays, clinical and economic evaluations, typically in the form of randomised controlled trials, are routine pre-requisites for the adoption of an innovative health care technology. In the 1960s, no such requirements existed. Even so, the accumulation of past evidence has now proved the clinical effectiveness of cervical screening, perhaps beyond reasonable doubt. Retrospective evaluations have also identified acceptable cost-effectiveness ratios [4], although these ratios generally appear inferior to those achievable for breast or colorectal cancer screening [5–7]. Screening those women with no previous screening history appears to be particularly cost-effective, even amongst an elderly population [4,8].

Whilst accepting the broad conclusion that cervical screening offers acceptable value for money, however, it is quite possible to speculate as to whether, on the basis

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of the evidence currently available, the existing screening protocols are actually optimal. For example, it has been conjectured that shorter screening intervals, of 3, as opposed to 5, years, would result in higher costs with no appreciable corresponding increase in yield, owing to the typically-long disease development time during the pre-carcinoma phases [9,10]. With respect to age of eligibility, existing protocols almost invariably recommend regular screening until subjects are well beyond the age of 60 years. However, it has recently been suggested that withdrawal from screening at an age as low as 50 years might be justifiable, under two sets of circumstances, each of which characterises low risk. These are, first, regular compliance with screening and a consistent prior record of negative results [11,12]. Second, the presence of certain strains of human papillomavirus (HPV) has been identified as a significant risk factor for the development of ICC [13,14], with the result that its absence at age 50 years or thereabouts might be taken as indicative of, again, low risk.

A model of the UK screening programme has recently been published, which offers predictions of the consequences of implementing a variety of alternative protocols which withdraw women at an earlier age than normal [15]. The model was based on mathematical representations of the clinical course of the disease [16], age-related mortality, test accuracy and management policy for those with positive results, and was calibrated using data from the medical literature. The authors speculated that resources would be saved as a result of earlier withdrawal, but noted that the question of the cost-effectiveness of the modelled protocols remained "beyond the scope of this study" (p. 359). The present paper, however, focuses on just this issue.

2. Patients and methods

The UK screening programme offers screening invitations every 3–5 years and withdraws women when they reach 65 years of age. The mathematical model generated simulated outcomes for three possible earlier ages at withdrawal, namely, 50, 55 and 60 years, and two scenarios were modelled for each age. These were, first, a negative smear prior to the specified age of potential withdrawal with three previous negative smears and, second, a negative smear after the specified age coupled with a negative test result for high risk types of HPV. Under each scenario and for each withdrawal age, results were presented for the expected annual number of smear tests, colposcopies required, HPV tests and cases of ICC, for a cohort of 100 000 women in a screening programme. The screening protocol, the cohort's age distribution and the screening compliance rate were as for the present UK female population. As would be anticipated, ages of withdrawal lower than 65 years resulted in fewer smears and colposcopies, but more HPV tests and expected cases of ICC. These additional cases would, naturally, require treatment. For any given age at withdrawal, HPV testing would enable a slightly reduced number of smear tests to be undertaken.

As the first stage in our analysis, we translated the events predicted by the model into cost implications for the UK's National Health Service (NHS). Cost data were obtained from independent costing studies. First, colposcopy costs were obtained from a study of patients in Nottingham diagnosed with pre-invasive neoplasia [17]. Two types of colposcopy were defined—the simple procedure, where findings were negative and where no further intervention would be required, and the complex case, where the presence of suspected cervical intraepithelial neoplasia (CIN) would entail biopsy and further treatment. This study also provided stage-specific, 5-year costs of treatment for ICC, and demonstrated that such costs were significantly lower for cancers detected and treated at stage 1. However, significant differences between costs of treatment for ICC at stages 2 through 4 were *not* demonstrated, with the result that we used a weighted average across the costs of these three stages.

From the second study [18], we obtained the costs of a routine smear test, which included general practice and laboratory costs, overheads, capital charges and programme administration. HPV testing has yet to be implemented in the NHS and is currently undergoing evaluation as a potential addition to the screening programme. Cost estimates, therefore, must necessarily be somewhat conjectural. We used an initial figure of two-thirds the costs of conventional cytology, as had been employed in an earlier HPV cost projection study [19].

Thus far we were able to estimate the expected NHS cost savings per case of ICC arising under each of the six early withdrawal scenarios, estimated at the mean values. However, given the variability of real-world parameters, we felt it important to undertake a sensitivity analysis. We used Monte Carlo simulation, with 5000 trials for each scenario. Given that cost-effectiveness ratios are conventionally expressed in terms of life-years lost or gained, we translated the expected additional cases of ICC occurring under each scenario into additional life-year losses relative to the base case scenario (exit at 65 years of age, irrespective of previous history). In our context, life-year losses resulting from early withdrawal depends on the time at which the additional ICCs might be expected to develop. This is necessarily something of a random process: a cancer might not develop until a woman is in her 80s, or it might develop immediately after she has been withdrawn from screening. Each possibility offers potential life-year losses, but the losses are greater for relatively-younger women. Life-years lost from early withdrawal

Table 1
Unit costs

Item	Cost (£)
Cervical smear	27
HPV test	18
Colposcopy—simple	50
Colposcopy—complex	511
Treatment, stage 1	9225
Treatment, stages 2–4	15 333

HPV, human papilloma virus.

were estimated as expected age at death from ICC, subtracted from normal life expectancy by age.

3. Results

Table 1 displays the baseline unit costs employed in the analysis, derived from the independent studies cited earlier and translated to 1998 values, using the NHS pay and prices index. In the sample considered by the source [17], 49% of ICCs presented at stage 1, and we incorporated this proportion into our estimates. In practice, the false-positive rate of cytology appears variable; rates as high as 50% have been reported [20]. For our basic results, we therefore assumed that 25% of colposcopies would be simple rather than complex, in that they would require no further investigation or treatment. Table 2 displays estimates both of the expected annual costs of the six modelled withdrawal scenarios and of the cost savings in comparison with the existing screening protocol. Note that these costs are un-discounted, and discounting at any positive rate would reduce the estimates of cost savings.

For the Monte Carlo simulations, five of the six cost parameters were allowed to vary as normal distributions, defined by the confidence intervals published in the data sources. The exception was the cost of the HPV test. As noted earlier, the use of HPV testing as a screening tool remains experimental in the UK and the method of administering the tests (if at all) has yet to be determined. If HPV testing were to be carried out as an independent programme, its costs could indeed be of the order indicated. However, were it to become a matter of routine, and conducted within the main cytological screening programme, the marginal costs would be very much lower than the value used in the Table 2 calculation. Accordingly, we defined this cost in the simulation as a uniform distribution between £5 (the approximate marginal cost of a basic, routine pathology investigation) and the base-line assumption of £18. The probability of simple colposcopies was also defined as a uniform distribution, bounded in this case between zero and 50%. The proportion of cancers requiring treatment at stage 1 was modelled as a triangular distribution about 50%, with a range of 33–67%. This functional form was selected on the assumption that the value which had been observed was also that most likely to occur in a general setting, although a degree of bounded variation might be expected, with decreasing probability.

Our estimates of life-year losses following the incidence of the additional ICCs occurring within the scenarios were made on the basis of recently-published data for England and Wales. For 1997, it has been estimated that the 1225 ICC deaths in that year caused a loss of 28 000 life-years [21], or 22.9 life-years per death. This average life-year loss is inevitably biased by the large individual losses incurred by younger and middle-aged women. The use of this loss estimate would be inappropriate for our simulations, because the additional ICCs brought about as a result of early withdrawal would presumably only develop after the withdrawal age specified by each scenario. Instead, we constructed the following framework.

The survival rate following a diagnosis of ICC depends crucially upon the age at presentation. For the ages of interest in our simulations, the 5-year survival rate is 61% for women aged 50–59 years, 54 and 39% for ages in the subsequent two decades, respectively, and 20% and below for those aged above 80 years [22]. We divided the post-withdrawal period into eight 5-year age cohorts, from 50–54 years through to 85 years and above. On the basis of the age-specific survival data, we assigned a linear trend to median life expectancy following ICC, from 8 years in the youngest cohort (50–54 years) through to 1 year in the oldest. Normal life

Table 2
Annual costs and cost savings, by scenario

Age at withdrawal (years)	Scenario	Smears	Colposcopy	HPV tests	Treatment	Total costs	Cost savings	Savings per additional cancer
65	Current	475 200	86 274	0	136 977	698 451		
60	3 −ve	459 000	84 295	0	139 514	682 809	15 642	78 211
60	HPV −ve	456 300	84 295	18 540	138 246	697 380	1070	10 704
55	3 −ve	413 100	78 359	0	149 660	641 119	57 332	57 332
55	HPV −ve	405 000	77 963	19 980	145 855	648 798	49 653	70 932
50	3 −ve	361 800	71 235	0	166 148	599 183	99 267	43 160
50	HPV −ve	353 700	71 235	20 880	158 539	604 354	94 097	55 351

HPV, human papilloma virus.

expectancies by age were available from published life tables [21], from which the estimates of life-years lost were obtained by subtraction. These ranged from 21.9 to 1.6 life-years, for the 50–54 years to the 85 years and above cohorts, respectively. These values were entered into the simulations as elements of a discrete probability distribution conditioned by the current relative incidence of ICC across the age cohorts [23]. The 75–79 year age cohort currently displays the highest rate, at 21.4 cases per 100 000 women.

Over and above the basic six scenarios in their mathematical model, the authors of the original paper provided predictions following parameter variation within their two withdrawal-at-50 years of age scenarios. In particular, they provided data for events and ICCs assuming that disease progression rates were either 20% higher or 20% lower, and that the prevalence of HPV beyond 50 years of age was 50% lower. We used these data for six further Monte Carlo simulations. Table 3 provides summary results for the 12 simulations. It should be recalled that, for all these estimates, costs and outcomes are undiscounted. It follows that, as long as costs are discounted at a higher rate than outcomes (as is conventional), these savings represent the maximum obtainable, given the remaining assumptions of the scenarios. Increasing the relative rate for cost discounting would progressively lower the value of cost savings.

In all of the Table 3 scenarios, the distributions of expected savings per life-year lost are highly skewed: means are consistently greater than medians. Standard deviations are uniformly high, and of similar magnitudes to the means. Across the scenarios, expected median savings never exceed £10 000 per life-year lost, means seldom rise above £15 000, and the probability of saving more than £20 000 per life-year lost rarely exceeds 20%. The instances where higher savings *do* occur are, of course, largely accounted for by trials where cancer incidence has been selected to occur at an advanced age, implying low denominators in the 'NHS cost savings per patient life-years lost' calculations. Comparisons of the variants for withdrawal at 50 years of age indicate that slower progression would increase the potential savings from these scenarios, whilst faster progression would actually generate additional costs whilst simultaneously giving rise to life-year losses. In most cases, the distribution of expected life-years lost is the biggest single contributor by far to the variation within each simulation. There are three exceptions, the first being withdrawal at 60 years of age using HPV testing, where the HPV test cost is the largest contributor. For the two increased progression, withdrawal-at-50 years of age scenarios, treatment costs by stage make an important minor contribution.

4. Discussion

Mathematical models of the impact of health care interventions are being published with increasing frequency in the medical literature. However, with respect to the form in which they appear, almost all, including the one considered here, lack transparency. Whilst the modelling process is invariably described and the results presented, the model itself is usually presented as a 'black box', in the sense that little precise indication is given of the underlying mathematical structure which

Table 3
Simulation results: expected savings per additional life-year lost

Age (years)	Scenario	Mean	Median	S.D.	% of trials with values		Contributions to variance (%):			
					<£0	>£20 000	Life-year losses	Cost of smear	Cost of HPV test	Treatment cost and stage
60	3 −ve	15 229	9725	14 359	0.0	14.5	97.3	2.2	–	0.0
60	HPV −ve	15 012	8860	17 384	0.5	20.4	52.6	2.2	44.6	0.1
55	3 −ve	10 218	5828	10 264	0.0	12.7	97.9	1.6	–	0.0
55	HPV −ve	14 433	8423	14 553	0.0	15.0	97.3	1.1	1.4	0.0
50	3 −ve	7105	4147	7534	0.0	11.4	98.1	1.5	–	0.0
50	HPV −ve	9808	5671	10 408	0.0	11.4	98.1	1.3	0.3	0.0
Disease progression reduced by 20%										
50	3 -ve	12 867	7533	13 633	0.0	11.4	98.2	1.5	–	0.0
50	HPV −ve	16 134	9353	17 107	0.0	23.9	98.2	1.2	0.3	0.0
Disease progression increased by 20%										
50	3 −ve	−2024	−1148	2264	100.0	0.0	87.2	5.0	–	7.7
50	HPV −ve	−2533	−1429	2868	100.0	0.0	84.7	5.4	2.9	7.0
HPV prevalence beyond 50 years = 50% of baseline assumption										
50	3 −ve	12 019	7032	12 743	0.0	11.4	98.1	1.4	–	0.0
50	HPV −ve	13 248	7661	14 060	0.0	12.7	98.1	1.2	0.3	0.0

HPV, human papilloma virus; S.D., standard deviation.

generates the inferences. Economists undertaking a cost-effectiveness analysis exogenous to a mathematical model, as we have done, must necessarily take the modelled results at face value. One can only work with that which has been published, although a detailed knowledge of the model's structure would undoubtedly have enabled us to refine our results further. For example, the published model shows that faster and slower disease progression rates give rise to larger and smaller numbers of ICCs, respectively. However, we suspect that differential progression rates would mean that the age distribution of the resulting ICCs would vary also. Faster progression could mean incidence at earlier ages, implying a higher number of life-years lost than that allowed by the distribution assumed in our simulations. The reverse would be the case when the progression rate is slower. Accepting this possibility, the two slow progression, withdrawal-at-50 years of age, scenarios would yield greater savings than those indicated in Table 3, whilst the rapid progression scenarios would entail even greater costs being incurred, whilst still losing life-years.

Accepting these limitations of exogenous modelling, what do our simulation results tell us? Here it is convenient to consider the matter in reverse. Let us suppose that any one of the base-case early-withdrawal scenarios were to be the current screening protocol, and we were considering whether to move to a 'new' protocol, namely, withdrawal at 65 years of age. From any one of these possible starting points, the move to withdrawal at 65 years would incur costs, but would yield life-year gains. The median or mean costs would typically be less than £10 000 or £15 000 per life-year gained, with costs rising above £20 000 occurring only in circumstances where ICCs could be assumed to present at advanced ages. Allowing for discounting, all these costs would be further reduced. It is unlikely that such cost-effectiveness estimates would be regarded as unacceptable by the NHS. Indeed, the NHS appears to be more than willing to provide interventions with considerably higher cost-effectiveness ratios at the present time, for example, in haemodialysis and heart surgery [24].

Were we actually to be considering a move in *this* direction — replacing one of the early withdrawal scenarios with screening until 65 years of age—the debate about the optimal age of withdrawal would be relatively simple to resolve, and would hardly require a modelling exercise. All of the early withdrawal scenarios are clinically less effective than the withdrawal-at-65 years of age protocol. Faced with the prospect of saving lives, therefore, a randomised controlled trial of the scenario and withdrawal at 65 years could be initiated, with a view to measuring both additional costs and life-year gains (survival, it will be recalled, was the greatest single source of variation in our simulations). The question could therefore be resolved experimentally.

Unfortunately, the trial approach is unlikely to offer the solution of appraising a move in the reverse direction, *away* from withdrawal at 65 years towards any protocol which inevitably generates life-year losses. It would almost certainly be deemed unethical to allow trial subjects to be randomised away from a regime of established effectiveness. Even if ethics could be circumnavigated, a practical problem remains. Cervical screening is currently provided to all eligible women at zero price under the NHS. If a trial of withdrawal-at-65 years versus an early withdrawal protocol *were* to be initiated, why would anyone volunteer to participate, given they might be randomised to a cohort which faces a higher risk of ICC?

It therefore seems probable that, in circumstances where savings would result only from a loss in clinical effectiveness, modelling is the only means available to resolve the issue of the optimality of the existing protocol. In this particular instance, our analysis appears to offer little support for replacing the current screening protocol with an early-withdrawal strategy. To re-iterate, if £10-20,000 per life-year gained is currently taken to represent reasonable value for money, then a saving of £10–20 000 per life-year lost would almost certainly be regarded as unreasonable.

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