Some considerations on the estimation of disease severity in the NHS cervical screening programme: PART II : Quantitative methods of estimating disease severity and progression potential

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Abstract

Current cytology and histology measurements are based on ordered categories and have a strong emphasis on providing information which naturally leads to a woman's management decision rather than the very best estimate of disease severity. In part I the problem of artificial cut-off points was discussed and a simple semi-quantitative solution to the problem was proposed which can be considered as an extension of BSCC terminology. In part II quantitative methods are proposed that are then used to predict the estimated progression probability to invasive cancer. The estimated progression probability based on cytology can be modified by examining other factors such as age, persistence, HPV status and number of cells with dyskaryosis. An estimate of progression probability is produced based on the histology information adjusted for age and lesion size and then a final estimate of progression probability based on both cytology and histology results.

Introduction

This is the second paper discussing the issue of the estimation of disease severity from cytological and histological information and the application of such measurements to research and routine screening. We are interested in achieving an estimation of the probability of progression to invasive cancer over a particular time period and we require an estimate of disease severity to help achieve that aim. By using an estimation of disease progression probability we can produce a continuous variable which can be used as such for research purposes, or divided into categories for different management options as required. Cytology can also have a role in the final estimation of disease severity, as colposcopy and histology are not as definitive a measure as would be desired [1].

The emphasis throughout the paper is on producing practical measurements that are likely to be acceptable to cytopathologists. To achieve this aim the method uses the semi-quantitative Grade number/Grade range (GN/GR) approach detailed in paper I and extends the method to produce estimated progression potentials. We can devise both simple and more complex methods of estimating disease progression probability. The advantage of simpler methods is that they are more likely to be acceptable to, and therefore used by, the clinical community. More complex methods requiring more difficult measurement or specialist software will therefore not be considered in this paper. The object is to produce an estimate of disease progression probability based on the cytological and histological

findings and then to use other factors such as age and lesion size to optimise that estimate. To do this we will develop a series of estimates of disease progression termed the estimated progression potential (EPP) for cytology (CEPP), for histology (HEPP) and for a weighted combination of cytology and histology (WEPP), together with some consideration of the errors in such estimates.

This paper principally represents an exploration of ideas around reporting cytology and histology as more quantitative measures. Many of the estimates given in the paper could certainly be improved, but it is beyond the scope of this particular paper to examine in detail all the factors, although it is hoped they are reasonable initial estimates.

Methods

An estimate of the probability of disease progression to invasive cancer can be obtained from the work of Holowaty et al [2]. The probability of various levels of cytology progressing to become invasive cancer is shown in table 1. The progression potential to invasive cancer for mild, moderate and severe dyskaryosis is 0.4, 1.2 & 3.9 per 100 women over 10 years respectively. We can assign the koilocytosis category a nominal value of 0.1 and the query invasive cancer category a nominal value of 100. The progression potential from histology findings is equivalent to the cytology progression if we consider that the definition of severe dyskaryosis is cytological changes suggestive of CIN3, moderate dyskaryosis is

cytological changes suggestive of CIN2 and mild dyskaryosis is cytological changes suggestive of CIN1 (see paper 1). We can also incorporate the work of McCredie et al [3] which followed the natural history of women with carcinoma in situ (CIS). The equivalent cytology could be referred to as HSIL favouring CIS (severe dyskaryosis favouring CIS). This study showed that women whose initial treatment of CIS was inadequate had a 12.6% chance of invasive cancer after 10 years and this information has been included in table 2a. The Grade Number (GN) of CIS can be given as 3.5 because by giving CIN3 a GN of 3 and CIN2 a GN of 2 the range of CIN3 is from 2.5 to 3.5 and therefore 3.5 represents CIS. The McCredie data is therefore included as a subgroup of grade 3 and the numerical scale is shown in table 2a. In practice the HSIL favouring CIS category is considered to be an optional category and numerically the GN value of 3.5 is exactly the same as that obtained from a slide where the reader was unable to decide between severe dyskaryosis and query invasive and opted for a probability of 50% severe dyskaryosis and 50% query invasive, which would also have a GN of 3.5. Of particular interest is that the progression potential of HSIL favouring CIS is estimated as more than 30x greater than that of mild dyskaryosis/CIN1. Furthermore it is of the order of 10x greater than lesions on the mild/moderate (LSIL/HSIL) or CIN1/2 cut-off point. Thus 'higher end' HSIL is very much more likely to progress to invasive cancer than 'lower end' HSIL and hence important to report for research purposes.

Estimating progression potential and allowing for estimation error

We require to estimate a lesions progression potential to invasive cancer, and also produce a measure of the uncertainty in the disease progression potential estimate. To do this we can use the calculated grade range and some modelling of the EPP and grade number using the data in table 2a. To get a good fit to the data two models have been produced. The regression equation linking the Grade Number GN of 1, 2 and 3 to the estimated progression probability (EPP) is:

$EPP = \exp((1.139 \times GN) - 2.068)$,

$R^2 = 99.96\%$

For the GN values of 3, 3.5 & 4 a different model has been fitted:

$EPP = 0.00000908 \times 57.607^{GN}$,

$R^2 = 99.95\%$

Values of the EPP have been calculated from GN values of 0.1-3.2 for the first model and from 3.3 to 4.0 for the second model. The relationship between GN and EPP is then given in a simple look up table format in table 2b. The simple modelling presented here suggest a substantial increase in progression probability occurs around a GN value of 3.25.

We can then apply this information to a slide reading. The best estimate of disease severity is given by the grade number (GN) value of the slide and the calculated grade range (CGR) introduced in paper I. Table 3 shows an example of a slide on the mild-moderate dyskaryosis border where the reader opted for moderate (HSIL) with a 60% probability, but with a lesser probability (40%) that the slide only showed mild dyskaryosis. The GN value is (60 x 2 + 40 x 1)/100 = 1.6 and the calculated grade range (CGR) = 1.5 (the average of 1 & 2) – 0.4 to 1.5 + 0.6 = 1.1-2.1. If the woman was referred to histology and the decision was on the border between CIN2 and CIN3 i.e. 50% chance CIN3 and 50% chance CIN2 then the GN value from histology is ((50 x 3) + (50 x 2))/100 = 2.5 and the CGR is from 2.5-0.5 to 2.5 + 0.5 i.e. from 2.0-3.0 (table 4).

Using the example above (shown in tables 3 and 4) and the look up table data shown in table 2b, if the cytology GN (and CGR) are 1.6 (1.1-2.1) the estimated progression potential from cytology (CEPP) is 0.78% (0.44% to 1.38%), that is a 0.78% chance of invasive cancer over the next 10 years with an range of uncertainty from 0.44% to 1.38%. Using the histology information (table 4) with the GN (CGR) data of 2.5 (2.0-3.0), the estimated progression probability from histology (HEPP) is 2.18% (1.23% to 3.85%)

To re-cap, the cytopathologist has examined a slide and decided that the sample is on the border between mild and moderate (also the border

between LSIL and HSIL) and has considered the sample to be slightly in favour of moderate (HSIL) and opted for a 60% probability of moderate and a 40% probability of mild. The estimated progression potential from cytology (CEPP) is 0.78% in the next 10 years with an error margin of 0.44% to 1.38%. What if the cytopathologist could really not decide, as is required in all current methods? The cytopathologist just gives a decision of 50:50 between mild and moderate leading to a GN(CGR) of 1.5 (1.0-2.0) and an estimated progression of 0.70% (0.40% to 1.20%) over the next 10 years. The decision to refer directly to colposcopy could be based on a GN value of 1.5 or a progression probability of 0.7% (similar to current practice), but the value can be altered by other considerations (see section below on allowing for other factors).

What is the CGR if the reader decides the slide shows clear evidence of say, severe dyskaryosis? The theoretical range of severe dyskaryosis is from a GN of 2.5 to 3.5. The GN values are therefore 3 (2.5 to 3.5) and from the look up table the progression probabilities are 3.9% (2.2%-13.2%).

Weighted estimated progression potential (WEPP)

If desired we can also calculate a weighted estimated progression potential based on using both the cytology and histology as estimates of disease severity. A simple method is to weight by a factor of 2:1 in favour of histology. This weighting ratio may be considered somewhat arbitrary,

however a ratio of 1:1 can be rejected as it gives equal weighting to the cytology, which would not be reasonable, and more than 3:1 can be rejected on the basis that the weighting is so much in favour of the histology result that it alone would be just as useful. Therefore ratios of 2:1, 2.5:1 and 3:1 could all be considered as practical and we will consider 2:1 in this paper. Using the examples shown in tables 3 & 4 with a CEPP of 0.78% and a HEPP of 2.18% the weighted estimated regression potential (WEPP) would be (2x2.18 + 1x0.78)/3 = 1.7% or about a 1 in 60 chance of progression to invasive cancer over the next 10 years. The advantage of the WEPP is that it takes into account all information on the estimated progression potential and is therefore likely to be the most robust estimate available from the combined cytology and histology information. It is important that the histology result is obtained independently and without direct reference to the cytology result to get the best WEPP estimate.

There is however a potential problem with the simple weighting used to create the WEPP, which occurs if no disease is detected at colposcopy/histology. For example if the CEPP were 12.6% and the HEPP was zero (i.e. nothing detected at colposcopy) the WEPP would still be 4.2%. Therefore the WEPP suggests a 1 in 24 chance of the disease progressing to invasive cancer over the next 10 years even though no disease is detected at colposcopy. If it is required that the detection of no disease at histology should lead to no progression probability (or a very low progression probability) then a solution is to use other weightings such as sqrt(CEPPxHEPP) where a HEPP of 0% would automatically lead to a

WEPP of 0%. To maintain a 2:1 weighting in favour of histology the WEPP would be sqrt((CEPP+HEPP)/2) x HEPP). The square root weighting system therefore has advantages and other weighting systems can be explored. Rather than reporting a HEPP of 0% if nothing is detected at colposcopy it may be better to use a nominal low value such as 0.1% to indicate very low risk.

Making allowance for other factors

We are trying to achieve a number that reflects the progression probability from the findings of both cytology and histology and in a manner that enables comparability across laboratories. In both methods we can regard both the cytology findings and the histology findings as providing evidence for that progression potential, even though the full estimate of the progression potential is only ever achievable for those women who are referred for colposcopy.

There are a number of other factors that can potentially make a difference to the progression potential. At cytology these include age, persistence, number of cells showing dyskaryosis and HPV test result. At histology these include age and lesion size. As a general rule the sum of all adjustments should equate to unity. For example, if a factor increases the risk by 2.0 and 10% of lesions have that factor, then the adjustment for all lesions not having that factor (90%) should be about 0.9 to balance the total risk of all lesions back to unity. The calculation of detailed adjustment

factors for all the factors mentioned is beyond the scope of this paper, but we will attempt to produce provisional adjustment factors that will require further refinement in future if the method becomes widely used. We can consider first the HPV test result and consider how to make adjustments.

Adjustment for HPV test result

We require to estimate the proportion of mild results and koilocytosis results which are HPV +ve. Let us assume that both 80% of mild results are HPV positive [4] and 80% of koilocytosis results are HPV positive. If the progression potential of all mild results is 0.4 per 100 women in 10 years (from table 1) and 80% of mild results are HPV +ve then if we assume that the progression potential of HPV negative women is close to zero then the progression potential of women with mild dyskaryosis who are HPV +ve must be 0.5 per 100 women in 10 years. In general we can suggest that if the HPV result is positive then the estimated progression potential from cytology is multiplied by 1.25 and if it is negative by zero. Using these factors the sum of the adjustments equals unity i.e. (1.25 x 80% + 0 x 20%)/100% = 1. If we consider the example of the simple CEPP estimate based on an estimated probability of 60% chance of moderate and 40% mild, then the CEPP was 0.78%. An HPV positive result will increase the CEPP to 0.78 x 1.25 = 1.0% and an HPV negative result will reduce the CEPP to zero (or close to zero).

We can go further and consider HPV type which is related to risk progression potential [5]. Lesions with HPV type 16 will have an increased risk (say 2.0), type 18,31,33 and 45 an intermediate risk (say 1.0), other HPV types a low risk (0.5) and no HPV a very low risk (0.1 or 0.0). Whilst further work is required on these risk estimates the concept is that different HPV types confer different progression potentials.

Adjustment for Persistence

In the absence of an HPV test, it is usual to repeat smears in women whose first test result is mild or borderline. In the case of mild dyskaryosis (which is of most interest in this present work) referral can be on first or second mild. If referral is on first mild then no correction factor is required, but if referral is on the second mild then the probability of progression estimate will increase. What correction factor would then be appropriate? To maintain the simplicity of the method we can suggest a correction factor the same as for mild with an HPV positive result. In other words we make the provisional assumption that the progression probability of a repeat mild result is the same as that of a first mild result which is HPV positive. This is based on the assumption that persistence implies a high probability of the presence of HPV. The cytology progression probability then increases from 0.78% to 1.0% using the example as before.

Adjustment for Age

Age is an important factor to consider, and laboratories can have different referral policies for women over 35 years and under 35 years of age. This is because of evidence of a higher progression potential in older than in younger women. Van Oortmarssen [6] suggested that under age 34, 84% of lesions will regress and over 34 this is only 40%. Expressing this data the other way we can estimate that under 34, 16% of lesions will progress and over 34, 60% of lesions progress. The NHSCSP screens women with a mean age of 40. If we assume a mean age under 34 of 27 and a mean age over 34 of 50, then we can estimate the progression probability using a simple regression as (1.91 x age) – 35.65. The actual values are shown in table 5. Correction for age can then be simply achieved by multiplying the progression probability by the appropriate correction factor. If we use only three groups of age to keep the method simple, then using correction factors of 0.5 for less than 35, 1.00 for 35-49 and 2.0 for 50+ is both reasonably in keeping with the data and simple.

Adjustment for number of cells

The number of dyskaryostic cells criteria is based on the work of Banville[7]. This study showed that only one in 17 women with mild dyskaryosis and subsequent high grade disease on follow up cytology or histology had 15 or

less dyskaryostic cells on the initial Thinprep slide. We can therefore suggest a lower progression potential if the dyskarysis evidence is only based on a few cells. As an initial estimate we can suggest multiplying the CEPP by 0.5 for samples with less than 15 dyskaryotic cells, by 1.0 for sample with between 15 and 50 and by 1.5 for samples showing greater than 50 dyskaryotic cells. Further work is required to produce better estimates.

Adjustment for lesion size (CIN3 component)

The size of a lesion and particularly the size of the CIN3 component is related to its progression potential [8] and invasive disease tends to arise from larger rather than smaller lesions. Provisionally we can assign a weighting of 1.0 to all cytological/histological findings where no CIN3 or <1mm CIN3 is detected at biopsy, a weighting of 1.5 to where 1-9mm of CIN3 is present at biopsy and a weighting of 2.0 where 10mm or more CIN3 is detected at biopsy. Arguably, the weighting of 1.0 should be marginally less than this to 'balance' the number of lesions that have reduced progression probabilities with those having increased progression probabilities. However, as a considerable majority of women referred will not have CIN3 this is probably not unreasonable and it keeps the numbers simple. Again, further work is required to improve these estimates.

Summary of adjustments

A summary of the suggested adjustments is shown in table 6. To show the use of the adjustments we can consider three examples. Firstly our example of a slide showing HSIL where the best estimate of disease severity was based on a 60% estimate of moderate and a 40% estimate of mild. The estimated progression potential was 0.78%. Let us consider that the woman was aged 52 yrs (correction factor x2.0) and this was her second mild smear (correction factor x1.25) and the number of dyskaryostic cells was greater than 50 (correction factor x1.5). The adjusted CEPP (ACEPP) would be 0.78 x 2.00 x 1.25 x 1.5 = 2.9%. If the women was referred to histology and the result was an estimate of 50:50 between CIN1 and CIN2 with a large lesion (but no CIN3 component) then the HEPP would be 0.70% which is multiplied by 2.0 to adjust for age = 1.4% and 1.0 for lesion size giving an adjusted HEPP (AHEPP) value of 1.4%. The WEPP is therefore sqrt(((2.9+1.4)/2) x 1.4) = 1.7%. The final estimate of disease progression to invasive cancer is therefore 1.7% over 10 years or a 1 in 58 chance of the disease becoming invasive over the next 10 years.

Referral to colposcopy based on the adjusted CEPP

The method facilitates referral to colposcopy to be based on the adjusted CEPP values and treatment on the WEPP values. The adjusted CEPP value

allows for age, persistence and number of cells showing dyskaryosis and therefore only a single estimate of disease progression probability is required. For example referral to colposcopy could reasonably be based on an ACEPP of 1%, suggesting a 1% probability of the woman having invasive cancer over the next 10 years. As an example a woman aged 35-49 with clear evidence of moderate dyskaryosis from 15-49 cells would have an estimated disease progression probability from cytology alone (ACEPP) of 1.2%.

Discussion

The CEPP/WEPP method gives a number which represents the best estimate of the woman's squamous pre-invasive lesion progressing to invasive cancer following cytology and then both cytology/histology results. The advantage of the WEPP is that it provides comparable information on the best estimate of disease severity and the progression probability of the disease. Furthermore the use of lower and upper ranges can give information on the degree of certainty surrounding that best estimate. The intention is (as much as possible) to divorce the estimate of disease severity from the management category. Although the principal aim of this work is to obtain more information for research purposes, in theory, clinicians would be free to decide at what level of cytological disease (CEPP) they would, for example, directly refer a woman to colposcopy, and artificial barriers caused by using only ordered categorical

variables such as mild, moderate or severe, or LSIL/HSIL are removed. Referral to colposcopy from an adjusted CEPP of 0.7% (a 1 in 143 chance of progression to invasive cancer over the next 10 years) or more would be very roughly in keeping with current practice.

Additional measures such as the correlation between cytology and histology could be studied in much more detail than is currently available and use could be made of graphical studies and correlation coefficients rather than the more limited Kappa statistics approaches required with categorical data. The relationship between HPV triage result and CEPP would also be of interest.

From a research perspective the relationship between the WEPP scores and particularly interval cancer rates could enable a better estimation of exactly what levels of disease need to be detected and referred to colposcopy to optimise the balance between sensitivity and specificity. Simply grading a specimen as HSIL or LSIL gives very little information as to what was actually being seen. The method as described is about producing an estimate of disease progression probability and not primarily intended as a substitute for detailed cytology description. Therefore cases that are broadly consistent with mild dyskaryosis/CIN1, but with some features that are suspicious of HSIL/CIN2 (which could be termed LSIL-H) could be graded as, for example, 70% probability of CIN1 and 30% CIN2 giving a GN of 1.3 and an EPP of 0.56%. The method also has great flexibility because the reader could opt for a 70% probability of CIN1, 20% CIN2 and

10% CIN3 giving an increased GN of 1.4 and an EPP of 0.62%. Such full information is also easy to encode on computer systems, where, for example, if we opted for a five triple digit sequence starting with grade number 0 (koilocytosis) and moving to grade number 4 (query invasive) the former (70% CIN1, 30% CIN2) would be 000 070 030 000 000 and the latter would be 000 070 030 010 000. A negative finding would simply be 000 000 000 000 000 and a clear finding of severe dyskaryosis 000 000 000 100 000. The same sequence could be used for the histology coding from 'HPV only' to invasive. It is therefore simple to encode such sophisticated information for research purposes. The inherent flexibility allows for any probability to be assigned, so for example if a reader was particularly uncertain about a particular slide and thought it had a 20% chance of just being inflammatory cellular change, but a 60% chance of being mild dyskaryosis, but also with a chance of 20% of being query invasive this can be catered for. It is 60% mild dyskaryosis and 20% query invasive, the 20% inflammatory cellular change conferring no progression probability, the GN is (60x1 + 20x4)/100 = 1.4 and the EPP is 0.62%. The code would be 000 060 000 000 020 because the 20% chance of inflammatory cellular change confers no progression probability. The method is therefore able to cope where the use of categories becomes almost impossible. The 'method' also has a number of stages which can be used independently, so that the GN part can be used as a standalone method without necessarily calculating the EPP etc.

There are a number of potential criticisms of the method which relate both to whether the method is practical to use and particularly how reliable are the estimates of disease progression that are obtained. There will always be some uncertainty in disease progression estimates as conducting randomised controlled trials would be unethical. The paper by McCredie et al [3] is unusual in that it does gives information on observed progression potential from inadequately treated CIS. It could be argued that even within the context of the data available the estimates shown in this paper may be improved upon, however it is beyond the scope of the present paper to do so. The range around the EPP values is an attempt to produce a simple and easy to calculate margin of error. In practice it is not clear how useful this will be and the method is clearly much quicker to calculate by hand just using the best estimate only. Alternatively it is simple to produce a routine to calculate the required numbers using a computer programme.

It is appreciated that the most difficult category is HSIL favouring CIS. This is an optional category that has been produced to help with the progression estimates from the McCredie data. It could be argued that the category is superfluous. Beyond its use to calculate table 2b the category can therefore be ignored if desired.

Whilst this paper very much represents a first attempt at producing a quantitative analysis, it is considered that the method as given could be directly applied. The method is hoped to be reasonably accurate, simple and useful. It is anticipated that such data could be included as a text field

in the computing systems and, for example, added to the annual KC61 returns as an annex. The method is readily open to future improvements and parts of the method e.g. the CEPP could be used separately to determine whether or not a woman should be directly referred to colposcopy.

In summary, the exploration of the direct use of progression estimates is an attempt to produce measures which relate directly to what is of utmost interest in cervical screening, namely the estimated disease progression probability. Knowledge of the estimated progression potential is advantageous to both making clinical management decisions as well as providing a more useful platform for further research.

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Glossary

Term	
Grade number – numerical estimate of cytology or histology disease severity	GN
Calculated grade range – range of estimate of disease severity	CGR
Estimated progression potential from cytology	CEPP
Estimated progression potential from cytology adjusted for other factors	ACEPP
Estimated progression potential from histology	HEPP
Estimated progression potential from histology adjusted for other factors	AHEPP
Estimated progression potential based on weighted cytology and histology	WEPP
Estimated progression potential based on weighted cytology and histology and adjusted for other factors	AWEPP

Table 1 Estimated progression probability to invasive cancer within 10 years from various grades of cytological abnormality (from Holowaty et al 1999)

	Cumulative actuarial rate of progression per 100 women within 10 years to invasive cancer of the cervix (95%CI)
Mild dysplasia	0.4 (0.3-0.5)
Moderate dysplasia	1.2 (0.9-1.5)
Severe dysplasia	3.9 (2.0-5.8)

Table 2a Cytology and histology estimated progression potential over 10 years

Cytology Grade	TBS style	Histology grade	Progression Potential (%)	Comment
Query invasive	HSIL favouring invasive	Invasive	100.0	Nominal value
Severe fav CIS*	HSIL favouring CIS	CIS	12.6	From McCredie et al
Severe dyskaryosis	HSIL favouring CIN3	CIN3	3.9	From Holowaty et al
Moderate dyskaryosis	HSIL favouring CIN2	CIN2	1.2	From Holowaty et al
Mild dyskaryosis	LSIL favouring CIN1	CIN1	0.4	From Holowaty et al
Koilocytosis	LSIL favouring Koilocytosis	HPV only	0.1	Nominal value

* **Severe dyskaryosis favouring 'advanced' CIN3 or CIS**

Table 2b Look-up table of Grade number (GN) value and estimated progression potential (EPP) calculated from regression models where EPP is the estimated probability of the lesions becoming invasive over the next 10 years.

GN	EPP	GN	EPP	GN	EPP	GN	EPP
0.1	0.14	1.1	0.44	2.1	1.38	3.1	4.32
0.2	0.16	1.2	0.50	2.2	1.55	3.2	4.84
0.3	0.18	1.3	0.56	2.3	1.74	3.3	5.86
0.4	0.20	1.4	0.62	2.4	1.95	3.4	8.78
0.5	0.22	1.5	0.70	2.5	2.18	3.5	13.2
0.6	0.25	1.6	0.78	2.6	2.44	3.6	19.8
0.7	0.28	1.7	0.88	2.7	2.74	3.7	29.6
0.8	0.31	1.8	0.98	2.8	3.07	3.8	44.5
0.9	0.35	1.9	1.10	2.9	3.44	3.9	66.8
1.0	0.39	2.0	1.23	3.0	3.85	4.0	100

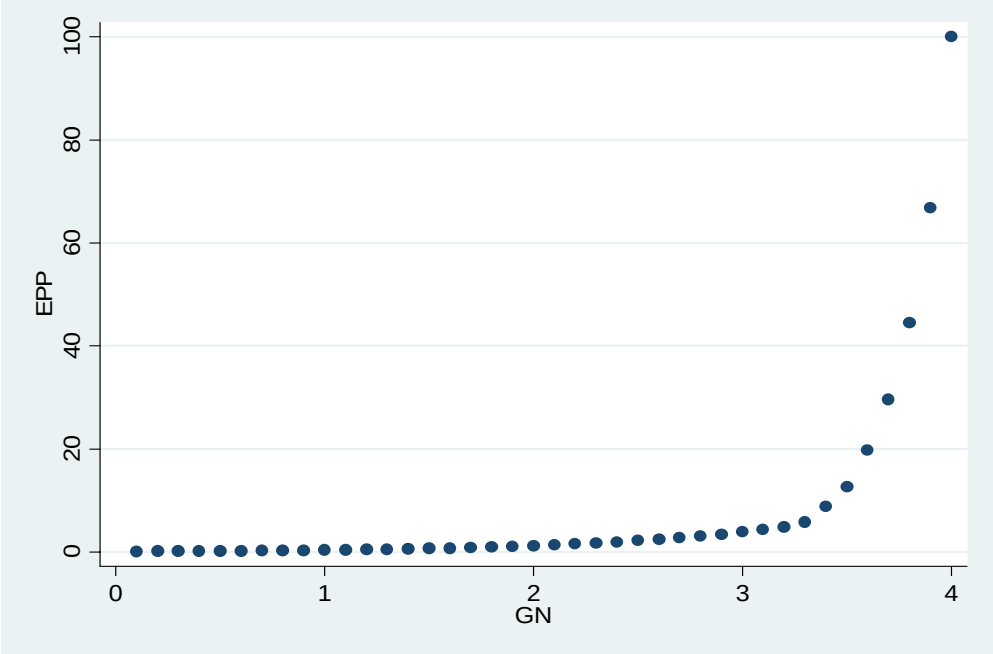

Table 3 Example of estimated progression potential (EPP) for cytology (CEPP) using method A

Cytology Grade TBS	Grade	Estimated probability of being in grade	Progression Potential
Query invasive	4		100
HSIL favouring CIS	*3.5**		*12.6*
HSIL favouring CIN3	3		3.9
HSIL favouring CIN2 (moderate)	2	60	1.2
LSIL favouring CIN1 (mild)	1	40	0.4
Koilocytosis (LSIL favouring koilocytosis)	0		0.1

GN (CGR) = 1.6 (1.1-2.1)
CEPP=0.78% (0.44-1.38) over 10 years

* Note the grade range for severe can be considered to be from 2.5 to 3.5 therefore the optional category of HSIL favouring CIS will have a grade of 3.5. It is numerically equivalent to a slide with an estimated probability of 50% severe/50% query invasive.

Table 4 Example of estimated progression potential (EPP) for histology (HEPP)

Histology Grade	Grade	Estimated probability of being in grade	Progression Potential
Invasive	4		100
CIN3	3	50	3.9
CIN2	2	50	1.2
CIN1	1		0.4
HPV only	0		0.1

GN (CGR) = 2.5(2.0-3.0)
HEPP = 2.18% (1.23%- 3.85%) over 10 years

Table 5 Correction factor for age by 5 year age-group

Age group	Mean age	Progression (%)	Correction factor*
25-29	27.5	16.9	0.41
30-34	32.5	26.4	0.65
35-39	37.5	36.0	0.88
40-44	42.5	45.5	1.12
45-49	47.5	55.1	1.35
50-54	52.5	64.6	1.59
55-59	57.5	74.2	1.82
60-64	62.5	83.7	2.05

* Progression divided by model progression at 40 (40.75%)

Table 6 Summary of adjustments to estimated progression potential (EPP)

Adjustment	Level	Multiply EPP by
Age*	<35	0.5
	35-49	1.0
	50+	2.0
Persistance	Mild/Koil (LSIL) 1st	1.0
	Mild/Koil (LSIL) 2nd	1.25
*HPV test***	*Negative*	*0.0 (or 0.1)*
	Positive	*1.25*
No of cells	<15	0.5
	15-49	1.0
	50+	1.5
Lesion size CIN3 component	None or <1mm of CIN3	1.0
	1-9mm CIN3	1.5
	10 or more mm CIN3	2.0

*Applies to CEPP and HEPP – all other measures to CEPP only. ** Alternative to persistence if HPV test has been undertaken.

Appendix: Detailed example of method including the range estimate

From cytology a 36 year old woman is found to have a sample with HSIL (more than 50 cells) estimated as having a 60% probability of severe dyskaryosis (HSIL favouring CIN3) and a 40% probability of moderate dyskaryosis (HSIL favouring CIN2). The GN is calculated as (60x3 + 40x2)/100 = 2.6. The CGR is calculated as 2.5-0.4 to 2.5+0.6= 2.1 to 3.1.

From the look-up table (2b) the CEPP is 2.44% (1.38% to 4.32%).
After adjusting for age and number of cells the progression probability is increased by 1.0 x 1.5 = 1.5 increasing the adjusted progression probability from cytology (ACEPP) to 3.66%(2.07% to 6.48%).

The woman is referred to histology and found to have a large lesion regarded as being 50:50 between CIN1 and CIN2. The GN is calculated as (50x1 + 50x2)/100 = 1.5 and the CGR as 1.5-0.5 to 1.5+0.5 = 1.0 to 2.0.

From the look up table the progression probability from histology (HEPP) = 0.70% (0.40% to 1.20%). After correcting for age and lesion size (1.0 x 1.0) = 1.0 the AHEPP=0.70% (0.40% to 1.20%).

The weighted estimated progression potential AWEPP can be calculated as the sqrt((3.66 +0.70)/2) x 0.70) = 1.24%.
The range can be similarly estimated as a lower limit of sqrt((2.07+0.40)/2)x0.40) = 0.70% and an upper limit of sqrt((6.48+1.2)/2)x1.2) = 2.15%.

Therefore the final estimate of progression potential is 1.24% (0.70% to 2.15%) over the next 10 years.