



A response to Ms Sandercock and Dr Burls regarding the methods used in the analysis for our first paper ‘Natural history of cervical neoplasia and risk of invasive cancer in women diagnosed with cervical intraepithelial neoplasia 3’

We published two papers reporting our findings from a review of the medical records of women diagnosed with cervical intraepithelial neoplasia 3 (CIN3) at National Women’s Hospital in 1955–76.^{1,2} The papers’ aims were quite different; so too were the methods, in particular the criteria identifying ‘treatment groups’ for the analyses, as explained below.

Sandercock and Burls wrote:³ ‘It is difficult to follow exactly what this paper [referring to *Lancet Oncology* 2008,¹ whose title is given above] was trying to prove, but as a means to demonstrate that conservative treatment led to worse outcomes, the methods are wholly inadequate.’ However, the aim of this paper (stated in the Summary and Introduction) was descriptive, namely to estimate the risk of cancer of the cervix or vaginal vault in two quite different circumstances: (i) when CIN3 had not been eradicated (‘inadequate treatment’); and (ii) when CIN3 had been eradicated on every occasion its presence had been indicated by positive cytology (‘adequate treatment’).

We drew attention to the contrast between these estimates which, not surprisingly, were very different but we made no formal comparison. Nor did we use the term ‘conservative treatment’; it is ambiguous, particularly in this context.

For the first aim of the *Lancet Oncology* paper, it was necessary to define a group of women in whom CIN3 persisted after the initial treatment, irrespective of the type of procedure. In practice, early follow-up cytology is the only way to identify these women. In this ‘inadequate treatment’ group, women were censored in the analysis whenever they had been treated ‘adequately’. Although post-procedure cytology could be considered an outcome for clinical purposes, it was not an outcome for this analysis—invasive cancer was the outcome.

Sandercock and Burls³ questioned our inclusion, in the ‘inadequate treatment’ group, of 4 women who developed cancer within 2 years of CIN3 diagnosis but who had no informative follow-up cytology, on the grounds that an outcome (cancer) had been used to categorise their treatment as ‘inadequate’. Before making the decision to include these women, we had considered what was likely to have been the status of their CIN3.

The three possibilities were: (i) that CIN3 had been completely removed by the initial treatment, followed by the appearance of *de novo* CIN3 which had progressed to invasive cancer in less than two years; (ii) that CIN3 had been incompletely removed, in which case our inclusion of these women was correct; or (iii) that invasive cancer was present at the time of CIN3 diagnosis but was not detected because of the limited nature of the biopsy. Given the short timeframe before the appearance of cancer, the

second or third possibilities were more likely. Whatever the circumstances, each of these women would have had CIN3 for part, if not all, of the less than 2 year period between their initial treatment and diagnosis of invasive cancer. Since our objective was to estimate the risk of progression from CIN3 to cancer, we were more likely to get an estimate closer to the true risk by including, rather than omitting, these 4 women.

It should be noted that the third possibility represents a risk inherent in the design of Dr Green's clinical study and for which the undertaking that 'if at any stage concern was felt for the safety of the patient, a cone biopsy would be performed',⁴ proved to be no safeguard.

The aim of our second paper in the *ANZJOG*² was to describe the 'medical experience' of women diagnosed at National Women's Hospital with CIN3, in particular during 1965–74 which were the main years of Dr Green's clinical study. For this analysis, women were grouped according to the type of initial treatment (defined as the most extensive surgical procedure in the 6 months after CIN3 diagnosis), irrespective of post-treatment cytology or subsequent treatment. It was here, in which the initial surgical management alone determined the groups for analysis, that we showed a clear difference in the risk of cancer attributable to withholding or delaying treatment with curative intent.

In this respect, I do not accept Dr Graeme Overton's interpretation⁵ of the numbers in McIndoe et al.⁶ Dr Overton used 'principal initial treatment' and 'initial treatment' for what McIndoe et al designated 'definitive management' or 'management' and which included 'later cone biopsy' and 'later total hysterectomy' (Tables 1 and 4).

McIndoe et al use the term 'initial treatment' only once (p 455, col 2, para 1). In this paragraph, of the 14 women in group 2 (i.e. those with continuing positive cytology) whose 'initial treatment' was said to be cone biopsy, 4 only had the cone biopsy 'later' (between 2 and 8 years after the original diagnosis of CIN3; Figures 2 and 3). They also stated (p 455, col 1, para 2) that all but 4 of the 131 group 2 women had a 'further biopsy' (range 1-19, median 6 years after the initial biopsy) to establish the final diagnosis. Some, but not all, of these 'further biopsies' were the same as the 'later' treatments in Tables 1 and 4.

No information was given in the tables about the duration of the delay between the first and later procedures. However, unpublished data from our analyses show that, for half of the women who were diagnosed with CIN3 in 1965–74, whose initial treatment was punch or wedge biopsy and who had positive cytology in the following 6–24 months, the first more extensive procedure (ring or cone biopsy, or hysterectomy), was delayed for more than 5 years. These subsequent procedures were probably equivalent to the 'later' treatments of McIndoe et al. Thus we have evidence, some indirect, that many 'later' treatments in Tables 1 and 4 of McIndoe et al were delayed several years after diagnosis of CIN3.

In Table 4 of McIndoe et al,⁶ a higher proportion of women in group 2 received cone biopsy or hysterectomy only as 'later' treatment or not at all (51%) than was the case for women in group 1, who did not have continuing positive cytology (22%), a finding in accord with our *ANZJOG* paper.²

Dr Green took a risk by delaying eradication of precancerous disease—the women in his clinical study paid a price.

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