Response to Elizabeth Overton’s comments about Ron Jones’ research

The treatment of women with cervical intraepithelial neoplasia 3 (CIN3) at National Women’s Hospital (NWH) in the years 1955-76 was subject to two quite separate analyses, the first published in 1984 by McIndoe et al, the second published in 2008 and 2010 by ourselves. Professor Ron Jones was an author of all three papers. Medical records of all women diagnosed with CIN3 at NWH in those years (not just those under Dr Green’s care) were the source of data for both analyses but as the inclusion and exclusion criteria were not quite the same, there were small differences in the final numbers. These differences are not important when considering the overall conclusions.

In the 1984 and 2010 papers, a principal outcome of interest was the difference in the risk of invasive cancer between two groups of women. In the 1984 paper the groups were defined according to whether or not women had persisting CIN3 on the basis of positive cytology two years after first diagnosis (irrespective of their treatment up to that time) whereas in the 2010 paper they were defined according to whether women, first diagnosed in the 1965-74 period, had treatment of curative intent within 6 months of first diagnosis (irrespective of their follow-up cytology). Thus the 1984 paper identified the risk resulting from failure to eradicate CIN3 within two years of diagnosis, while the 2010 paper identified the risk due to withholding or delaying treatment of curative intent.

Mrs Overton’s letter claims to identify a major discrepancy between the 1984 and the 2010 papers in the numbers of women with respect to their initial treatment. She continues the line of reasoning used by her husband Dr Graeme Overton, and adopted by Ms Sandercock and Dr Burls, in earlier letters to NZMJ. The flaw in Dr Overton’s reasoning was identified and explained in a previous letter, and is given again below.

Mrs Overton writes: ‘The 1984 McIndoe Paper states that of the 948 women with grade 3 cervical dysplasia reviewed, 1955–76, 923 had principal initial treatment of hysterectomy or cone excision of cervix and 25 punch or wedge biopsies.’

- Her reference (#2) identifies four places in the 1984 paper to support this statement. These are, each with the actual wording used in the paper for what she has represented as ‘principal initial treatment’:
  - Page 452, Table 1: ‘Definitive management …’
  - Page 453, para 6 and page 454, para 4: In both cases the words in the text are ‘The principal management…’
  - Page 455, para 2: This paragraph is concerned with how a final diagnosis was reached in women, with the word ‘initial’ used to describe the type of biopsy on which the earlier diagnosis had been based, the wording being ‘… after the initial biopsy diagnosis of CIS, by …’ (with the various types of initial biopsy being specified).
The 1984 paper does not define ‘definitive’ or ‘principal’ management but it would appear that these terms were interchangeable. It does not use either together with the word ‘initial’.

The term ‘initial treatment’ was used only once in the 1984 paper, when referring to 29 group 2 women who developed invasive carcinoma and whose detailed management was depicted in Figures 2 and 3. Of these women 14 were said to have had ‘initial treatment’ by cone biopsy and 6 by hysterectomy. However, of these 14 so-called ‘initial’ cone biopsies, 4 had been delayed 2 to 8 years after first diagnosis of CIN3.7

Table 4 of the 1984 paper, headed ‘Detailed patient management’, gave treatment information separately for women in group 1 and group 2. Women who received either cone biopsy or total hysterectomy as ‘later’ treatment were identified but ‘later’ was not defined. Of the women in group 1, 78% (n=637) had hysterectomy, amputation of the cervix or cone biopsy as their first treatment, 20% (n=165) as later treatment and 2% (n=15) had no more than a punch or wedge biopsy. By contrast, the respective numbers for women in group 2 were 49% (n=64), 44% (n=57) and 8% (n=10).

Hence, both Dr and Mrs Overton have wrongly used the term ‘principal initial treatment’ to include management that was not necessarily ‘initial’ (by the definition used in the 2010 paper) and, at least in some cases, had been delayed for some years after the original diagnosis.

Another less important difference between the numbers in the two papers is that the 1984 paper included ring biopsy (a shallow cone biopsy) with cone biopsy whereas it was separately categorised in the 2010 paper, as Dr Green had described it as not being definitive treatment.8 That this distinction was justified is clear from Table 3b and Figure 2b of the 2010 paper, which show that the risk of invasive cancer following initial management by ring biopsy was intermediate between that following cone biopsy on the one hand and punch or wedge biopsy on the other.

Mrs Overton states that the 2010 paper ‘claims to be the ‘final word’ to silence all critics of the 1984 McIndoe Paper’.

The inverted commas imply that this is a quotation from the paper. Nowhere in the paper is such a claim made; indeed, it makes no reference to ‘critics of the 1984 McIndoe paper’.

She asserts that the 2010 paper states ‘of the 948 women reviewed by McIndoe in the years 1955–76, 428 women, in the years 1965–74, had initial management in which treatment of ‘curative intent’ was deliberately withheld in unethical experiments.’

There is no such statement.

Of the 1063 women diagnosed with CIN3 at NWH in 1955-76, 422 (not 428 – probably a typographical error) were newly diagnosed in 1965-74.3 These 422 women comprised the group in whom we compared the outcomes according to their initial management (that is, within 6 months of CIN3 diagnosis) – 215 received treatment of curative intent (cone biopsy, amputation of cervix or hysterectomy), 72 a ring biopsy, 127 no more than a punch or wedge biopsy and 8 a biopsy of unknown type (Tables 2b & 3b). Thus, it was in only some of the 422 women that treatment of curative intent was deliberately withheld.
Certainly, the number of women (127) who had initial management of punch or wedge biopsy in the 2010 paper is higher than the number (25) whose definitive management was described as punch and/or wedge biopsy in the 1984 paper. However, while the 25 women had never had a procedure that was more extensive than a punch or wedge biopsy, the 127 women had no more than a punch or wedge biopsy within 6 months of their diagnosis but may have had a more extensive procedure subsequently.

Many of the 222 later treatments included under the heading of ‘definitive management’ in the 1984 paper would not have been counted as ‘initial management’ in the 2010 paper.

Mrs Overton writes: ‘Simple arithmetic confirms that it is not possible to have 422 women with treatment of “curative intent withheld” in 948 women which the 1984 McIndoe Paper states 923 had initial treatments of cone excision or hysterectomy, i.e. on their own 2010 definition ‘treatment of curative intent’

- As shown above, this is based on the incorrect assumption that definitions in the 2010 paper applied also to the 1984 paper.
  - ‘Definitive’ or principal’ management (1984) was not the same as ‘initial’ management (2010).
  - McIndoe et al included ring biopsy with cone biopsy (1984), while ring biopsy was categorized separately in the 2010 paper.
  - Procedures performed more than 6 months after the original diagnosis were taken into account in the 1984, but not in the 2010, paper.

She concludes that ‘the 2010 statistics are damaging fiction in my opinion.’

- As we have shown, she has misunderstood the published information on which her letter is said to be based. These derogatory remarks about the 2010 paper are without foundation.

Our 2010 paper showed that the group of women with CIN3 not treated promptly with curative intent had a substantially increased risk of invasive cancer even though some subsequently received such treatment.

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References:


