A response to Professor Bryder’s comments on ‘Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3’

In her recent NZMJ Editorial, Professor Linda Bryder raised six points regarding this paper which was published in Aust & NZ J Obstet & Gynaecol. These points are listed below, each with an explanation.

1. The definition of ‘treatment of curative intent’

We deemed ‘curative intent’ to encompass procedures designed to eradicate all tissue with cervical intraepithelial neoplasia, grade 3 (CIN3), an outcome that could only be achieved with some certainty by hysterectomy, amputation of the cervix or cone biopsy. Dr Green himself pointed out in 1962 that ring biopsy, a slightly less extensive procedure than cone biopsy, was not ‘definitive therapy’ for CIN3. We also provided a textbook reference supporting this definition as it applied to international practice at the time. This is not to deny that lesser procedures sometimes, in the case of ring biopsy quite often, effect a ‘cure’; moreover, there is no guarantee of ‘cure’ with treatment of curative intent, as can be verified by careful examination of Figure 1 of our Lancet Oncology paper.

2. Why was 1974, rather than 1970, chosen as the last year of the ‘clinical study’?

Initially, we examined the data from 1955-76 (the period covered by the McIndoe paper) in four 5-year periods and one 2-year period; the 1st and 2nd, and the 3rd and 4th periods, were combined to simplify presentation of the data. Figure 1 of the ANZJOG article does indeed show that there was a lower proportion of women in Green’s ‘core group’ in the years 1971-74 (just under 20%) than in 1966-1970 (about 50%). However, the effect of choosing 1974 instead of 1970 as the last year was to reduce the difference in outcomes for the women according to the period of CIN3 diagnosis (Tables 2a and 3a) but to make little difference to outcomes according to initial management (Tables 2b and 3b). 1975 was the year an internal (National Women’s Hospital) inquiry released its report into the conduct of the clinical study. Our data show that, of women newly diagnosed with CIN3 in 1975-76, 14 (5.5%) received no more than a punch or wedge biopsy as initial management (Table 1) and 30 (11.7%) had untreated positive smears during follow-up (Table 2a). Clearly, the practice of withholding or delaying curative treatment was abandoned gradually, not abruptly.

3. No evidence that patient records reviewed were Green’s patients

Our analysis included all women who were newly diagnosed with CIN3 at National Women’s Hospital in the years 1955 to 1976, irrespective of their clinician, provided they satisfied the inclusion criteria outlined in the paper.
We did not record the name of the treating doctor. However, it is fair to assume that whenever curative treatment was withheld or delayed, it was in accordance with the policy of Dr Green’s clinical study. Our aim was to ascertain the effect on women of different forms of initial management rather than to compare outcomes according to individual clinicians. It should be noted that we analysed follow-up interventions only for 10 years after initial diagnosis of CIN3 (i.e. no later than 1984 for women included in the clinical study).

4. Were women in the early 1960s more likely to be unscreened than in the period 1965–74?

As pap smears were introduced into New Zealand only in 1955, the cytological abnormality that prompted the histopathological diagnosis of CIN3 would have been picked up in the first pap smear for nearly all women diagnosed in the 1955–64 period, at least in the first few years. However, as time went on, an increasing proportion of women would have had a previous pap smear.

5. A retrospective study cannot prove unethical behaviour which implies intent not to do the best for one’s patients

In our ANZJOG paper, we did not make the claim that its findings proved unethical behaviour. What we did acknowledge in the Background of the Abstract and in the Introduction was the unethical nature of the clinical study from which our data were derived, and supported this with independent references. The wording was included to satisfy requirements pertaining to publication of findings from studies considered unethical.

In my view, clinical research that involves giving or withholding a medical intervention cannot be deemed ethical on good intentions alone. In 1964 the Declaration of Helsinki stated:

(i) “Clinical research cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject” (section 1, paragraph 3) and “Every clinical research project should be preceded by careful assessment of inherent risks in comparison to foreseeable benefits to the subject or to others” (section 1, paragraph 4).

(ii) “… the doctor should obtain the patient’s freely given consent after the patient has been given a full explanation” (section 2, paragraph 1).

We did not record information relating to informed consent. However, our results show that the inherent risk of invasive cervical or vaginal cancer was high, not low as claimed by Dr Green. Moreover, Figure 2(b) in our ANZJOG paper shows that half of the cancers in women managed initially by no more than a punch or wedge biopsy were diagnosed within 5 years of the CIN3 diagnosis. These are data by which to judge whether the importance of the objective (not having a cone biopsy) was in proportion to the inherent risk (invasive cancer).
6. Where is the authors’ evidence that ‘follow-up’ biopsies were often intended to exclude invasive cancer rather than to diagnose and treat CIN3?  

Our wording was: “These observations are consistent with the findings of the judicial inquiry that follow-up biopsies often were intended to exclude invasive cancer rather than to diagnose and treat CIN3, …” (Discussion, 2nd paragraph). In relation to our own findings, we stated: “…inclusion in this clinical study subjected women to many medical interventions designed to observe rather than treat their cervical intraepithelial neoplasia,…” (Discussion, 1st paragraph). The evidence for this was, in the ‘core group’, the approximately 4-fold increase in frequency of positive smears (indicating persistent or recurrent CIN3) that were not followed by a treatment with curative intent, and of follow-up biopsies (Table 2b). Of the follow-up biopsies taken from women in this group in the 10-years 1965–74, only one-quarter were ‘with curative intent’ (unpublished data).

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References: