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Original Article

Consequences in women of participating in a study of the natural history of cervical intraepithelial neoplasia 3

Margaret R.E. MCCREDIE,[1] Charlotte PAUL,[1] Katrina J. SHARPLES,[1] Judith BARANYAI,[2] Gabriele MEDLEY,[3] David C.G. SKEGG[1] and Ronald W. JONES[4]

[1]*Department of Preventive and Social Medicine, University of Otago, Dunedin,* [2]*Lab Plus, Auckland District Health Board, Auckland, New Zealand,* [3]*Melbourne Pathology, Collingwood, Victoria, Australia, and* [4]*Gynecological Oncology Department, National Women's Hospital, Auckland, New Zealand*

Background: A retrospective cohort study was performed in 1063 women diagnosed with cervical intraepithelial neoplasia grade 3 (CIN3) (previously termed carcinoma *in situ* – CIS) in the National Women's Hospital, Auckland, New Zealand. The study describes the clinical management and outcomes for women with CIN3 diagnosed in the decade of 1965–1974, when treatment with curative intent was withheld in an unethical clinical study of the natural history of CIS. A comparison is made with women who were diagnosed earlier (1955–1964) and later (1975–1976).
Aims: The aim of the study is to record the medical encounters, frequency and management of cytological abnormalities and the occurrence of invasive cancers. The medical records, cytology and histopathology were reviewed and data linked with cancer and death registers.
Results: Women diagnosed with CIN3 in 1965–1974 (n = 422), compared with those diagnosed earlier (n = 385) or later (n = 256): (i) were less likely to have initial treatment with curative intent (51% vs 95 and 85%, respectively); (ii) had more follow-up biopsies ($P < 0.0005$); (iii) were more likely to have positive cytology during follow-up ($P < 0.005$) and positive smears that were *not* followed within six months by a treatment with curative intent ($P < 0.005$); and (iv) experienced a higher risk of cancer of the cervix or vaginal vault (RR = 3.3 compared with the first period, 95% CI: 1.7–5.3). Among women diagnosed in 1965–1974, those initially managed by punch or wedge biopsy alone had a cancer risk ten times (95% CI: 3.9–25.7) higher than women initially treated with curative intent.
Conclusions: During the 'clinical study' (1965–1974), women underwent numerous interventions that were aimed to observe rather than treat their condition, and their risk of cancer was substantially increased.

Key words: cervical intraepithelial neoplasia 3, natural history, unethical research.

Introduction

By the 1960s, the concept that cervical cancer arises from an intraepithelial precursor lesion was generally accepted, although it had not been subjected to rigorous testing.[1] Dr GH Green at National Women's Hospital in Auckland was unconvinced,[2] and with the approval of the Hospital Medical Committee in 1966, he commenced a clinical study of the natural history of carcinoma *in situ*[3] (CIS; now included, together with severe dysplasia, in the definition of cervical intraepithelial neoplasia, grade 3 – CIN3). In this clinical study, women with CIN3 received a diagnostic biopsy to confirm the diagnosis and exclude invasive cancer. These women were closely observed, but treatment with curative intent was withheld initially, and often later. While analyses of the ethical failures of the clinical study have been influential in improving processes for the proper conduct of research,[4–6] and a number of independent studies have been published using the data,[7–10] no account has been given previously of the direct effects on the women who participated.

The clinical study was started in 1965[11] (before the 1966 approval), but not all women with a diagnosis of CIN3 were included. Some women with persistent or recurrent abnormalities after initial cone biopsy or hysterectomy were also included in the study,[11] and some with microinvasive carcinoma of the cervix,[11] or with vaginal[11] or vulval[7] intraepithelial neoplasia, were followed without treatment. Informed consent was not sought from the women.[12]

Following a complaint to the hospital authorities by two medical colleagues in 1973, a hospital committee reviewed

Correspondence: Professor Ronald W. Jones, Department of Gynaecological Oncology, National Women's Hospital, Greenlane Clinical Centre, Private Bag 92024 Auckland 1142, New Zealand. Emails: MBarrios@adhb.govt.nz; rwjones@xtra.co.nz

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the management of a small number of women. From the time of the committee's report in 1975, few new patients with CIN3 were admitted to the clinical study.

Although Dr Green claimed his clinical study confirmed that CIN3 rarely progresses to invasive cancer,[11,13–15] McIndoe *et al.* published in 1984 an independent analysis of outcomes in women diagnosed with CIN3 at National Women's Hospital in 1955–1976, which demonstrated a 25-fold increased risk of cervical or vaginal vault cancer in those women with persistent cytological abnormalities, compared with women whose cytology during follow-up was normal.[8]

We have recently extended this approach to re-examine the natural history (or invasive potential) of CIN3 and the outcome after conventional clinical management among patients at National Women's Hospital.[9]

Allegations concerning the management of women with CIN3[16] led in 1987 to a judicial inquiry, which reviewed the conduct of the clinical study.[12,17] During this inquiry, the clinical records of all women were assessed and an independent clinical review was recommended where there was any doubt about the adequacy of treatment.[12,17]

In 2009, a history of this so called 'unfortunate experiment' was published,[18] in which many of the findings of the judicial inquiry were rejected using the arguments that Dr Green was motivated principally by a justified desire to avoid unnecessary surgery, and that there were no adverse consequences for patients.

In this study, we re-examine the data from National Women's Hospital to describe the direct consequences in women of participating in the clinical study, in particular, the number and type of medical interventions and the risk of invasive cancer. We have compiled a comprehensive analysis of the management and follow-up of women with CIN3 during 1955–1976, which includes the decade of the clinical study (1965–1974) together with two periods for comparison (1955–1964 and 1975–1976). This differs from our previous natural history analysis,[9] which censored follow-up for women when they received adequate treatment, and therefore does not represent the full picture of the women's experience. We describe women's medical encounters (including for cytology smears and biopsies), the frequency and management of positive cytology and the occurrence of, and deaths from, invasive cancers of the cervix and vaginal vault, according to the period of first diagnosis of CIN3. For women who were diagnosed in the decade 1965–1974, we contrast their experience and outcome according to the type of initial management.

Methods

This study was approved by the Auckland Regional Ethics Committee. Details of the methods have been published elsewhere.[9] Of the 1229 women newly diagnosed with CIN3 at National Women's Hospital during 1955–1976, 1063 (86%) were included in the present study cohort. Women were excluded because of missing medical records (n = 48), insufficient information (n = 6), a previous or concurrent diagnosis of invasive cancer of the cervix, vagina or vulva (n = 7), an initial diagnosis made elsewhere (n = 34) or a diagnosis after histological review that was not CIN3 (n = 71). Hence, we excluded all women with a review diagnosis of stage 1A cervical carcinoma or worse.

The Victorian Cytology Service in Melbourne, Australia reviewed the cytology using the current Australian Modified Bethesda system, 'blind' with respect to the original report.[10] We deemed cytology to be 'positive' if assessed as Papanicolaou class 3, 4 or 5, or Modified Bethesda possible or definite high grade abnormality. Cytology in the first six months after a procedure was excluded as non-informative because reparative changes may give rise to false positive smears.[19]

During the period 1955–1976, treatments aimed at eradicating CIN3 comprised hysterectomy, amputation of the cervix and cone biopsy (termed 'treatments with curative intent'). Procedures intended for diagnosis rather than cure included wedge and punch biopsy. Ring biopsy, defined as removing a shallow cone <2 cm[20] or <1.5 cm[11] deep, was not considered as a 'definitive' therapy,[20] a view consistent with practice elsewhere at that time.[21]

The description of medical encounters during follow-up was restricted to the first ten years after diagnosis of CIN3, to allow for different lengths of follow-up and changes in practice following the judicial inquiry.[12,17] During the clinical study, microinvasive carcinoma of the cervix was managed in the same way as cervical carcinoma *in situ*.[11] Hence, we counted medical encounters after a subsequent diagnosis of FIGO[22] stage 1A disease but not after a diagnosis of invasive cervical cancer that was FIGO stage 1B or greater.

Cancer outcomes reported in this study are invasive cancer of the cervix (ICD-9 180), vagina (ICD-9 184.0), vulva (ICD-9 184.4) or anus (ICD-9 154.2 or 154.3). Cancers were identified through medical records, histopathological review or linkage with cancer and death registers. The original lists were linked with population-based cancer registers of New Zealand and Queensland and New South Wales in Australia and with death registers of New Zealand and Australia.

Follow-up continued until death or 31 December 2000. Names and addresses of women not known to have died were linked with electronic electoral rolls. The last date on which women were known to be alive and free of lower genital tract cancer was before 31 December 2000 for 187 women (18%; representing 8.2% of total follow-up time), and they were assumed to be alive and free of cancer on that date.

Statistical analysis

Comparisons of rates of smears and biopsies were made using Poisson regression with robust estimates of standard error. Associations between categorical variables were evaluated using the Chi-squared test. Cumulative incidence of (first) cancer of the cervix or vaginal vault was estimated using the Kaplan–Meier method, with between-group comparisons using the log-rank test and Cox regression. Hazard ratios estimated by Cox regression are referred to

here as relative risks (RR). Standardised incidence ratios (SIR) and mortality ratios (SMR) were based on age- and period-specific rates for the New Zealand population for the years 1955–2000; indirect, rather than direct, standardisation was used because of the small number of cancers in each period. Analyses were performed using STATA Statistical Software Release 10 (StataCorp. 2007. College Station, Texas, USA: Stata Corporation).

Results

Among 1063 women diagnosed with CIN3 at National Women's Hospital during 1955–1976, the median age at diagnosis was 38 (range 21–74) in 1955–1964, 38 (16–64) in 1965–1974 and 32 (19–72) in 1975–1976. Women in 1965–1974 were more likely to be of Maori ethnicity (11% compared with 6% in the other two diagnostic periods) and to have had at least five children (21% compared with 17% in 1955–1964 and 11% in 1975–1976).

The initial diagnostic procedure varied considerably by the period of diagnosis (Table 1). An incidental finding of CIN3 in hysterectomy specimens or in the amputated cervix was uncommon but occurred most frequently in 1955–1964 (7%), when 80% of the women had a procedure with curative intent as their initial procedure compared with 30% in 1965–1974 and 55% in 1975–1976 (Table 1).

Initial management (defined as the most extensive procedure within six months of diagnosis) was a procedure with curative intent for 95% of women in 1955–1964 and 85% in 1975–1976, but for only 51% of women in 1965–1974 (Table 1). Within each diagnostic period, initial management also varied substantially (Fig. 1). No cone biopsies were recorded before 1958, the year in which the hospital policy directed that cone biopsy was to be the preferred initial treatment for CIN3. From 1959 to 1963, a majority of women underwent cone biopsy, which reached its maximum frequency (85%) in 1963. Apart from a single case in 1960, initial management by punch biopsy made its first appearance in 1965 (the first year of the clinical study),

Figure 1 Initial management by calendar year of diagnosis of CIN3.

Table 1 Initial management in women with CIN3, by period of diagnosis

	Period of CIN3 diagnosis		
	1955–1964 (*N* = 385) *n* (%)	1965–1974 (*N* = 422) *n* (%)	1975–1976 (*N* = 256) *n* (%)
Initial diagnostic procedure			
Hysterectomy/amputation of cervix	27 (7.0)	14 (3.3)	6 (2.3)
Cone biopsy	280 (72.7)	114 (27.0)	136 (53.1)
Ring biopsy*	52 (13.5)	46 (10.9)	17 (6.6)
Wedge biopsy	3 (0.8)	22 (5.2)	1 (0.4)
Punch biopsy	9 (2.3)	215 (50.9)	82 (32.0)
Biopsy of unknown type	14 (3.6)	11 (2.6)	14 (5.5)
Most extensive procedure within six months of CIN3 diagnosis			
Hysterectomy/amputation of cervix	138 (35.8)	37 (8.8)	25 (9.8)
Cone biopsy	226 (58.7)	178 (42.2)	193 (75.4)
Ring biopsy	15 (3.9)	72 (17.1)	22 (8.6)
Wedge biopsy	1 (0.3)	26 (6.2)	1 (0.4)
Punch biopsy	1 (0.3)	101 (23.9)	13 (5.1)
Biopsy of unknown type	4 (1.0)	8 (1.9)	2 (0.8)
Cytology 6–24 months after initial management			
Informative smear available	323 (83.9)	364 (86.3)	205 (80.1)
Possible or definite high-grade abnormality†	58 (18.0)	165 (45.3)	45 (22.0)

*Ring, defined as a shallow cone biopsy <2 cm (2) or <1.5 cm deep (5).
†Percentage of those with an informative smear.
CIN3, cervical intraepithelial neoplasia grade 3.

and comprised about 50% of cases in 1966, 1968 and 1969. From 1969 to 1974, initial management was a wedge or ring biopsy in 20–40% of women.

The presence of CIN3 at the excision margin was not recorded in the histopathology reports for punch or wedge biopsies, and often not for ring or cone biopsies.[9] However, the presence of residual CIN3 could be assessed from informative cytology 6–24 months after initial management in more than 80% of women from each diagnostic period (Table 1). Of women with an informative smear, the percentage with at least one positive smear was 45% in 1965–1974 compared with 18 and 22% in 1955–1964 and 1975–1976, respectively ($P < 0.0005$).

The likelihood of ever having received treatment with curative intent continued to differ according to the period of CIN3 diagnosis. After ten years, 96% of women from the 1955–1964 group and 91% of women from the 1975–1976 group, but only 71% of those diagnosed in 1965–1974, had undergone a procedure with curative intent either initially or subsequently.

Table 2(a) shows that, although the frequency of smear-taking was about one per year for each group of women, the women diagnosed in 1965–1974 were more likely to have had five or more positive smears (14% compared with 3 and 1% in the earlier and later periods, $P = 0.005$), and at least one positive smear which was not followed by a procedure with curative intent (32% compared with 8 and 12%, respectively; $P < 0.005$). Follow-up biopsies also were more frequent in women diagnosed in 1965–1974 ($P < 0.0001$; Table 2a).

To identify as closely as possible women who had been included in Dr Green's clinical study, we subdivided the women first diagnosed in 1965–1974 according to initial management (Table 2b). We deemed that women who received only a punch or wedge biopsy as their initial management were the 'core' clinical study group ($n = 127$). Among this group, 33% had five or more positive smears during follow-up (compared with 5% in women initially treated with curative intent), and 61% had at least one positive smear that was not followed by a procedure with curative intent (compared with 15% in those initially treated with curative intent). The core group also had 4.6 times as many biopsies as women initially treated with curative intent.

Women diagnosed in 1965–1974 who received initial management with curative intent (Table 2b) were broadly similar to those diagnosed in 1955–1964 or 1975–1976

Table 2 Medical encounters during first ten years of follow-up in women with CIN3, by (a) period of diagnosis and (b) initial management

	(a) Period of CIN3 diagnosis (all women)			(b) Initial management* (women diagnosed in 1965–1974 only)		
	1955–1964 ($N = 385$)	1965–1974 ($N = 422$)	1975–1976 ($N = 256$)	Hysterectomy, amputation of cervix or cone biopsy ($N = 215$)	Ring biopsy ($N = 72$)	Punch or wedge biopsy ($N = 127$)
Cervical/vaginal smears						
Average rate per woman per year†	1.1	1.1	0.8	1.0	1.1	1.3
Number (%) of women with positive smears‡						
No smears	315 (81.8)	239 (56.6)	202 (78.9)	159 (74.0)	36 (50.0)	36 (28.3)
1–4 smears	59 (15.3)	122 (28.9)	51 (19.9)	46 (21.4)	27 (37.5)	49 (38.6)
5+ smears	11 (2.9)	61 (14.4)	3 (1.2)	10 (4.7)	9 (12.5)	42 (33.1)
Untreated positive smears§						
Number (%) of women with ≥1	32 (8.3)	135 (32.0)	30 (11.7)	32 (14.9)	23 (31.9)	78 (61.4)
RR (95% CI)	1.0 (reference)	3.8 (2.7–5.5)	1.4 (0.9–2.3)	1.0 (reference)	2.1 (1.3–3.4)	4.1 (2.9–5.8)
Biopsies of any type (after initial six months)						
Average rate per woman per year	0.02	0.06	0.02	0.03	0.05	0.12
RR (95% CI)	1.0 (reference)	3.2 (2.2–4.7)	1.0 (0.6–1.7)	1.0 (reference)	2.0 (1.2–3.3)	4.6 (3.1–6.9)
Number (%) of women with biopsies						
No biopsies	341 (88.8)	279 (66.1)	224 (87.5)	179 (83.3)	48 (66.7)	48 (37.8)
1 biopsy	31 (8.1)	87 (20.6)	22 (8.6)	22 (10.2)	16 (22.2)	45 (35.4)
2 biopsies	7 (1.8)	35 (8.3)	8 (3.1)	10 (4.7)	5 (6.9)	20 (15.7)
3+ biopsies	6 (1.6)	21 (5.0)	2 (0.8)	4 (1.9)	3 (4.2)	14 (11.0)

*Most extensive procedure within six months of CIN3 diagnosis; excludes eight women whose initial management was a biopsy of unknown type.

†From Poisson regression.

‡Possible or definite high grade cytological abnormality, excluding smears within six months after a procedure.

§A positive smear not followed by a procedure of curative intent within six months.

CIN3, cervical intraepithelial neoplasia grade 3; RR, relative risk; 95% CI, 95% confidence interval.

(Table 2a) with regard to the frequency of positive smears, of positive smears not followed by a procedure with curative intent and of biopsies during follow-up.

Invasive cancer of the cervix or vagina was reported in 70 women, three of whom had cancer at both sites (Table 3a). All 13 vaginal cancers were in the vault. More than 70% of cervical cancers in each period were stage 1 when first diagnosed. The cancer was detected within one year of CIN3 diagnosis in four women, all from 1965 to 1974.

The cumulative risk of cancer during 30 years of follow-up was the highest for women diagnosed with CIN3 in 1965–1974 (log-rank $P < 0.0005$; Fig. 2a). The age-adjusted relative risk (in comparison with women diagnosed with CIN3 in 1955–1964) was 3.3 (95% CI: 1.8–5.8; Table 3a); further adjustment for ethnicity and parity did not alter the estimate (data not shown). Schoenfeld residual plots suggested that the relative risk declined after 15 years in women diagnosed with CIN3 in 1965–1974, but data were limited and an additional time-dependent covariate allowing the relative risk to change after ten years was not statistically significant ($P = 0.08$).

Compared with the New Zealand population, each group of women had an increased risk of cancer of the cervix or vagina, about 19-fold for those diagnosed with CIN3 in 1965–1974, and about fourfold for women diagnosed in 1955–1964 or 1975–1976 (Table 3a).

There were no statistically significant differences in cancer mortality across the three periods, but numbers were small. Compared with the New Zealand population, the risk of death from cervical or vaginal cancer was raised fivefold for women diagnosed with CIN3 in 1955–1964, ninefold for those diagnosed in 1965–1974 and fourfold for those diagnosed in 1976–1975 (Table 3a).

Among women diagnosed with CIN3 in 1965–1974, the risk of cancer was ten times higher in the core group (initial management: punch or wedge biopsy) than in women from the same period treated initially with curative intent (Table 3b and Fig. 2b). Compared with the general

Table 3 Cancer of cervix or vaginal vault in women with CIN3 diagnosed in 1965–1974, by (a) period of diagnosis and (b) initial management

	(a) Period of CIN3 diagnosis (all women)			(b) Initial management* (women diagnosed in 1965–1974 only)		
	1955–1964 ($N = 385$)	1965–1974 ($N = 422$)	1975–1976 ($N = 256$)	Hysterectomy, amputation of cervix or cone biopsy ($N = 215$)	Ring biopsy ($N = 72$)	Punch or wedge biopsy ($N = 127$)
Median duration of follow-up (years)	36.5	28.0	24.7	28.3	27.5	28.8
Cancer of cervix or vaginal vault						
No. with cancer of cervix	12	44	4	3	7	32
No. with cancer of vaginal vault†	5	6	2	2	1	3
Crude rate per 100 000 woman-years (95% CI)	123 (74–205)	473 (358–626)	101 (45–224)	89 (37–213)	471 (236–942)	1186 (848–1660)
RR (95% CI)‡	1.0 (reference)	3.3 (1.8–5.8)	0.7 (0.3–1.9)	1.0 (reference)	4.4 (1.4–13.6)	10.0 (3.9–25.7)
SIR (95% CI)§	4.5 (2.7–7.5)	18.5 (14.0–24.4)	4.0 (1.8–8.9)	3.4 (1.4–8.2)	18.4 (9.2–36.9)	47.2 (33.7–66.0)
Deaths from cancer of cervix or vaginal vault						
No. deaths	8	11	2	1	2	8
Crude rate per 100 000 woman-years (95% CI)	65 (3–130)	99 (55–178)	33 (8–133)	17.5 (2.5–124)	112 (28–447)	231 (116–462)
RR (95% CI)	1.0 (reference)	1.6 (0.6–4.0)	0.8 (0.2–4.4)	—	—	—
SIR (95% CI)	4.7 (2.4–9.4)	8.9 (4.9–16.0)	3.9 (0.9–15.5)	1.5 (0.2–10.9)	10.7 (2.7–42.7)	20.9 (10.4–41.8)

*Most extensive procedure within six months of CIN3 diagnosis; excludes eight women whose initial treatment was a biopsy of unknown type.

†Two women from 1955 to 1964 period and 1 from 1965 to 1974 had been diagnosed previously with cancer of the cervix.

‡Stratified by age group at CIN3 diagnosis.

§Standardised incidence and mortality ratios, calculated using age- and period-specific incidence or mortality rates of cancer of cervix and vagina (not restricted to vault) for the New Zealand population for the period 1955–2000. The estimate is conservative as women who developed cancer at both sites are only counted once in the observed numbers, but could be included twice in the expected numbers.

CIN3, cervical intraepithelial neoplasia grade 3; RR, relative risk; 95% CI, 95% confidence interval.

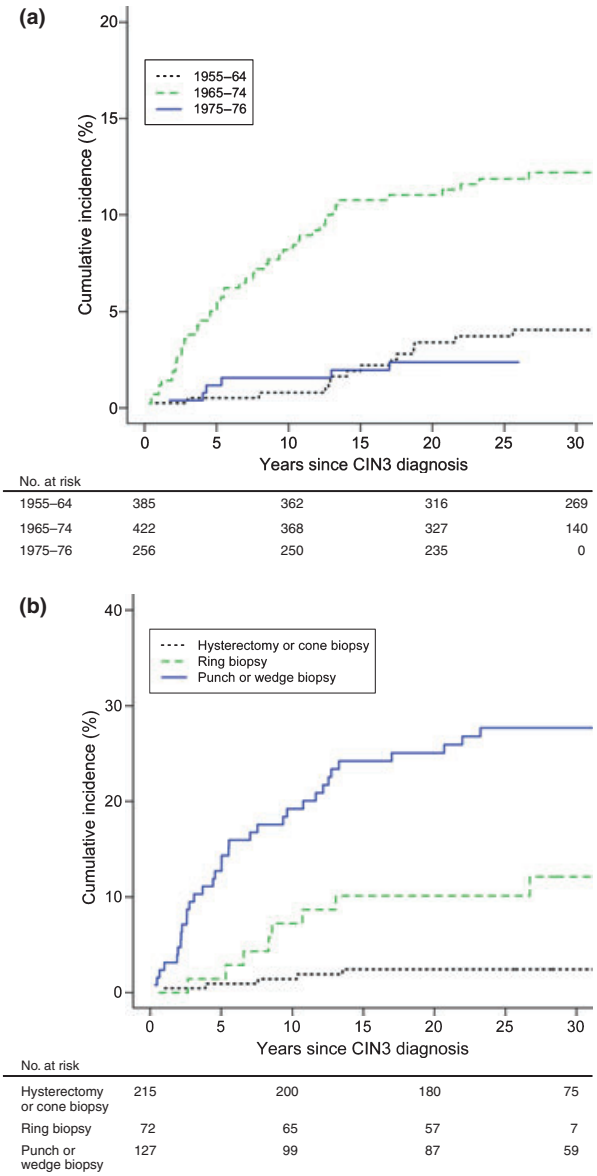

Figure 2 Cumulative incidence of cancer of the cervix or vaginal vault by (a) period of diagnosis of CIN3 and (b) initial management (women diagnosed in 1965–1974 only).

population, the risks were raised 47 times and 3.4 times, respectively, for these two groups. The numbers of deaths were too small to make reliable comparisons, but eight of the 11 deaths occurred in the core group (n = 127) compared with one among the women treated initially with curative intent (n = 215).

The risk of cancer of the cervix or vaginal vault among women diagnosed with CIN3 in 1965–1974 who were treated initially with curative intent (Table 3b) was similar to that among women diagnosed in 1955–1964 and 1975–1976 (Table 3a).

Numbers of vulval and anal cancers were too small for comparison between groups. In the entire cohort of 1063 women, seven were diagnosed with vulval cancer and five with anal cancer, the SIR being 8.9 (95% CI: 3.6–18.5) and 13.2 (95% CI: 4.3–30.7), respectively.

Discussion

Dr Green's clinical study of the natural history of CIN3 in Auckland has proved to be a landmark investigation in relation to the natural history of cervical intraepithelial neoplasia and in the field of medical ethics. While data on cancer outcomes have been reported by McIndoe *et al.*,[8] and, more recently, ourselves,[9] the medical experience of the women is reported here for the first time. Our findings show that inclusion in this clinical study subjected women to many medical interventions designed to observe rather than treat their cervical intraepithelial neoplasia, and increased their risk of developing cancer of the cervix or vaginal vault.

The greater numbers of subsequent biopsies that were performed on women in the core group (who received only a punch or wedge biopsy initially) attest to their assiduous follow-up. Consistent with the objectives of the study, conventional warning signs were often not acted upon, as is clear from the proportion of women with repeatedly positive smears or with positive smears that were not followed by a procedure with curative intent. 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, and with case histories describing how treatment was repeatedly withheld from individual women.[12,17,23,24] Moreover, it is clear that the policy of the clinical study was responsible for the excess of inappropriate follow-up interventions for women diagnosed in 1965–1974, as they occurred principally among women whose initial management was no more than a punch or wedge biopsy.

The risk of invasive cancer of the cervix or vaginal vault was significantly higher among women diagnosed with CIN3 in 1965–1974, even though women diagnosed in the earlier period (1955–1964) were chiefly an unscreened population,[25] and therefore their disease is likely to have been present for a longer period prior to diagnosis. The mortality from cervical or vaginal vault cancer that was more similar between periods may have been due to the intensive follow-up of women as, at all times, the majority of cancers were detected at a relatively early stage. Even so, in the clinical study, treatment was withheld from some women with a diagnosis of microinvasive carcinoma.[11]

Among women diagnosed with CIN3 in 1965–1974, the incidence of invasive cancer was ten times greater in the core group (who received only a punch or wedge biopsy initially) than in women treated initially with curative intent. This comparison is valid only for these women; a generalisable estimate of risk for untreated women that takes into account further treatment during follow-up has been reported elsewhere.[9] Nearly all cancer deaths among women diagnosed in this period occurred in the core group.

The incidence of vulval and anal cancers in women diagnosed with CIN3 during 1955–1976 was nine times

and 13 times the New Zealand population rate, respectively. Swedish women aged 18–50 years diagnosed with CIN3 during 1968–2004 had an incidence of vulval and anal cancers that was 2.2 and 4.7 times, respectively, the rates in women who had never been diagnosed with CIN3.[26]

It is unlikely that bias affected the comparisons according to time period or initial management. Careful reanalysis of medical records and examination of histopathology slides and cytology smears, with excellent retrieval of material stored for up to 40 years,[9,10] has provided an objective and systematic account of the medical experience of these women. The extent of follow-up information was enhanced by a policy of (at least) annual visits to the hospital for examinations and smears. Moreover, we restricted the description of each woman's clinical management to the ten years following her diagnosis, so that the analysis was not influenced either by the longer follow-up for women in earlier diagnostic periods or by the review and recall of women following the judicial inquiry.[17,27] The total number of medical interventions would have been much higher than shown by this truncated analysis. As ascertainment of cancers encompassed only women who remained in New Zealand or who lived in two Australian states, there may have been additional cancers among the few who emigrated elsewhere.

The consequences of the clinical study were profound for the women who participated. When initial treatment of curative intent was withheld, their lives were seriously disrupted by the need to attend hospital for numerous additional medical interventions that would not have been necessary had treatment of curative intent been offered at the outset. Moreover, they had a substantially increased incidence of invasive cancer, with all the emotional stress and physical symptoms that the diagnosis of genital malignancy entails. We have published these findings to document and to acknowledge the harm suffered by these women.

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Contribution to authorship

There were seven authors, all of whom contributed to the analysis, interpretation of data and approved the final version of the manuscript. RJ, DS, CP, MM, JB and KS conceived and designed the study. MM and RJ supervised the conduct of the study. JB carried out the histopathology review. GM supervised and participated in the cytology review. KS did the statistical analyses, and all authors viewed the full results of statistical analyses and can take responsibility for the integrity of the data and the accuracy of the data analysis. MM drafted the manuscript – all authors contributed to its development and critical revision. MM is the guarantor.

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