Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study

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Summary

Background The invasive potential of cervical intraepithelial neoplasia 3 (CIN3; also termed stage 0 carcinoma) has been poorly defined. At the National Women's Hospital, Auckland, New Zealand, treatment of CIN3 was withheld from a substantial number of women between 1965 and 1974 as part of an unethical clinical study. The resulting variation in management allows comparison of the long-term risk of invasive cancer of the cervix in women whose lesion was minimally disturbed with those who had adequate initial treatment followed by conventional management. We aimed to estimate the long-term risk of invasive cancer in these two groups of women. A judicial inquiry referred for independent clinical review in 1988 all women for whom there remained doubt about the adequacy of their management.

Methods Between February, 2001, and December, 2004, medical records, cytology, and histopathology were reviewed for all women with CIN3 diagnosed between 1955 and 1976, whose treatment was reviewed by judicial inquiry and whose medical records could be located, and linkages were done with cancer and death registers and electoral rolls. To take into account the probability that the CIN3 lesion had been completely removed, we classified adequacy of treatment by type of procedure, presence of CIN3 at the excision margin, and subsequent cytology. The primary outcome was cumulative incidence of invasive cancer of the cervix or vaginal vault. Follow-up continued until death or Dec 31, 2000, whichever came first. Analyses accounted for procedures during follow-up.

Findings 1229 women whose treatment was reviewed by the judicial inquiry in 1987–88 were included. Of these, 48 records (4%) could not be located and 47 women (4%) did not meet the inclusion criteria. At histopathological review, a further 71 (6% of 1134) women were excluded because the review diagnosis was not CIN3. We identified outcomes in the remaining 1063 (86% of 1229) women diagnosed with CIN3 at the hospital in 1955–76. In 143 women managed only by punch or wedge biopsy, cumulative incidence of invasive cancer of the cervix or vaginal vault was 31·3% (95% CI 22·7–42·3) at 30 years, and 50·3% (37·3–64·9) in the subset of 92 such women who had persistent disease within 24 months. However, cancer risk at 30 years was only 0·7% (0·3–1·9) in 593 women whose initial treatment was deemed adequate or probably adequate, and whose treatment for recurrent disease was conventional.

Interpretation This study provides the most valid direct estimates yet available of the rate of progression from CIN3 to invasive cancer. Women with untreated CIN3 are at high risk of cervical cancer, whereas the risk is very low in women treated conventionally throughout.

Funding Cancer Society of New Zealand, Wellington, New Zealand.

Lancet Oncol 2008; 9: 425–34

Published Online
April 14, 2008
DOI:10.1016/S1470-2045(08)70103-7

See Reflection and Reaction page 404

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Introduction

Cervical cancer is the second most common cancer affecting women worldwide.[1] Cytological screening programmes aim to detect precursor lesions, known as cervical intraepithelial neoplasia (CIN), and treat these to prevent the onset of invasive cancer. Cervical screening has not been assessed by randomised trials, so controversy has remained for half a century about the effectiveness of different screening policies. Assumptions about the natural history of CIN underpin recommendations about frequency of cervical screening, yet uncertainty surrounds the estimates of invasive potential of CIN.[2]

A unique opportunity has arisen from a clinical study of the natural history of cervical carcinoma in situ (CIS) at the National Women's Hospital, Auckland, New Zealand, in which treatment of curative intent was withheld or delayed for many women who were first diagnosed between 1965 and 1974.[3,4] CIS is now included, together with severe dysplasia, in the definition of CIN grade 3 (CIN3; full thickness involvement of the epithelium with dysplastic cells, but with no signs of invasion into the stroma; also termed stage 0 carcinoma of the cervix).[5] That clinical study was initiated by G H Green who obtained permission from senior medical staff at the hospital to attempt to verify his premise that CIS was not a precursor of invasive cancer.[3] From 1965, some women with CIS received no treatment of curative intent after a diagnostic biopsy, often no more extensive than punch or wedge, the purpose of which was to confirm the diagnosis and exclude invasive cancer.[6] Women were followed up with regular clinical, cytological, and sometimes colposcopic examinations, but persistent abnormalities were frequently not considered an indication

Cytology*	Hysterectomy or amputation of cervix			Cone biopsy†			Ring biopsy‡			Punch or wedge biopsy	Unknown biopsy		
	CIN3 in margins			CIN3 in margins			CIN3 in margins				CIN3 in margins		
	Absent	Unknown	Present	Absent	Unknown	Present	Absent	Unknown	Present		Absent	Unknown	Present
Normal, benign, or class 2	76	61	0	184	86	74	15	20	14	24	1	3	0
No cytology	24	27§	1	35	17	18	4	6	3	19§	0	4§	2
2R¶ or low grade	3	4	0	24	12	15	1	4	1	10	0	1	0
Class 3, 4, or 5, or high grade	2	2	0	30	46	56	4	23	14	90	0	2	1

Adequate | Probably adequate | Probably inadequate | Inadequate

***Figure 1*: Classification of adequacy of treatment according to the type of procedure, presence of CIN3 at the excision margins, and cytology 6–24 months after the procedure**
Numbers are n. Classification was applied to all procedures but numbers refer to the most adequate procedure within 6 months of diagnosis for the 1063 women. *Classified either according to Papanicolaou or the modified Bethesda grading system;[9] cytology in the first 6 months after any procedure was excluded because reparative changes may give rise to false-positive smears.[11] †Includes a small number of large loop excision of the transformation zone procedures when definition was applied to subsequent treatment. ‡Ring defined as a shallow cone biopsy <2 cm[12] or <1·5 cm deep[6] and not considered definitive treatment.[12] §Four women (two in the wedge or punch biopsy group and one in each of the other groups) were deemed to have had inadequate initial treatment as they had no informative smears but developed invasive cancer within 2 years of diagnosis. ¶Code used by the cytology laboratory at National Women's Hospital to indicate the presence of atypical cells suggestive of dysplasia (but less than carcinoma in situ) with the recommendation for a repeat smear.

for treatment. Additionally, treatment of curative intent was withheld from some women diagnosed with CIS in the years before 1965, despite cytological evidence of persistent or recurrent disease. The clinical study was not a randomised clinical trial, not all women with CIS were under Green's care, and no records exist of which women were chosen for that study which, however, was never formally ended. In response to the concerns of some clinicians in 1973, a working party was set up and, from the time of its report in 1975,[4] few women with CIS were referred to the study. Therefore, the decade 1965 to 1974 can be taken as the operative period of recruitment to the study, although some women remained without curative treatment after 1975.

A judicial inquiry held in 1987–88 concluded that the study was unethical because treatment was withheld without consent, monitoring of outcomes was inadequate, and the study was not ended when clinicians raised concerns.[4,7] Additionally, the judicial inquiry referred for independent clinical review in 1988 all women for whom there was any doubt about the adequacy of their management. One of the recommendations from the inquiry was that the histological and other material at the National Women's Hospital "should be available for properly planned and approved research and teaching".[4] The opportunity to learn from this experience is enhanced by the fact that meticulous records were kept and many women had repeated cervical smears and biopsies, with the latter often intended for diagnosis rather than cure.[4]

An independent analysis by McIndoe and colleagues[8] in 1984 that used data from women diagnosed at the hospital over the period 1955–76, assessed the risk of cancer of the cervix or vaginal vault in women with, and those without, persistent positive cytology 2 years after the diagnosis of cervical CIS. Their estimate of risk in women with evidence of persistent disease has become a standard reference on the invasive potential of CIN3.

We have extended this approach by reviewing inclusion criteria, histological diagnoses, and cytological findings; updating diagnostic criteria and terminology; taking into account both initial and follow-up treatment; and extending the period of follow-up. We estimated the invasive potential of CIN3 by establishing the long-term risk of invasive cancer of the cervix or vaginal vault in women with persisting disease as defined by positive cytology within 2 years after initial treatment (first aim) and in women who had minimum disturbance of their lesion (ie, punch or wedge biopsy; second aim). We also aimed to estimate the long-term risk of cancer in women who received adequate treatment initially and conventional management thereafter (third aim), approximating current clinical practice

Methods

Patients and procedures

We considered for inclusion all women diagnosed histologically with CIS alone or CIS with microinvasion at National Women's Hospital between Jan 1, 1955, and Dec 31, 1976, the main period of concern to the judicial inquiry.[4] These comprised: those whose names were on the clinic register at National Women's Hospital (n=1194), or who were included in the McIndoe lists, referred to in Appendix 3 of the New Zealand Cervical Cancer Inquiry report[4] (an additional n=35). Between February, 2001, and April, 2002, medical records were reviewed for all women whose medical records could be located. We excluded women without a histopathology report for the initial diagnostic biopsy, those for whom the initial diagnosis of CIS was made outside the National Women's Hospital,

those whose diagnostic material had been removed from the National Women's Hospital, or those who had a previous or concurrent diagnosis of invasive cancer of the cervix, vagina, or vulva. The study entry point for the evaluable women was the date of the first procedure diagnosing CIS. If a second procedure had been done within 3 months and its histopathology report raised the possibility of more advanced disease (n=14), this second procedure was deemed to be the entry point.

To establish whether the original diagnosis of CIS could be accepted as CIN3 by today's criteria, JB undertook a blind histopathological review of the initial histopathology for a random sample of 121 (13% of 948) women who were in the McIndoe study[8] by use of the current staging system of the International Federation of Gynecology and Obstetrics (FIGO).[5] JB also blindly reviewed the initial histopathology for all women (n=231) who potentially could have been included in the current analysis but had been excluded for various reasons by McIndoe and colleagues[8] and, not blindly, whenever the possibility of microinvasion or invasion was raised in the diagnostic histopathology report (n=35). Material was retrieved for all but two (<1%) women.

Since the size of the biopsy was unknown and for some women there was incomplete excision, an estimate of the minimum area of CIN3 was made by use of the standard block width for 125 (89%) of 141 cone biopsies and 26 (72%) of 36 ring biopsies in the random blind histopathology review.

The Papanicolaou grading system for cytology, used at the time these women attended the National Women's Hospital, has been superseded. The Victorian Cytology Service in Melbourne, VIC, Australia, undertook a cytology review between October, 2002, and May, 2003, by use of their current Australian Modified Bethesda system, blind with respect to the original report.[9] Material selected for review comprised: all smears taken during the first 24 months after the initial diagnosis of CIS for all women; and all subsequent smears for women whose medical records showed that they later developed microinvasive or invasive cancer of the lower genital tract. In the 4930 slides that were reviewed, there was good agreement between original and review coding (kappa 0·79).[9] Whenever available, the review cytology during the first 24 months was used to categorise severity of abnormality in our analyses.

All information on procedures and smears was extracted from the medical records of the National Women's Hospital where most treatment occurred during follow-up. Information on cytology and procedures done elsewhere was often recorded in these records.

A list of all women considered for this study was linked in mid-2003 with: cancer registers of New Zealand and two Australian states—Queensland and New South Wales (of New Zealanders who migrate to Australia, about two-thirds live in these two states;[10] most of the remainder live in Victoria whose registry has restricted access to data for

***Panel:* Classification of adequacy of treatment according to the type of procedure, presence of CIN3 at the excision margin, and cytology* 6–24 months after the procedure**

Adequate

- After hysterectomy or amputation of the cervix, if CIN3 was known to be absent from the excision margin, and cytology was normal, benign, or class 2, or there was no cytology
- After cone† biopsy, if CIN3 was known to be absent from the excision margin, and cytology was normal, benign, or class 2
- After ring‡ biopsy, if CIN3 was known to be absent from the excision margin, and cytology was normal, benign, or class 2

Probably adequate

- After hysterectomy or amputation of the cervix, if CIN3 was known to be absent from the excision margin, and cytology was 2R§ or low-grade
- After hysterectomy or amputation of the cervix, if it was not known whether CIN3 was present or absent from the excision margin, and cytology was normal, benign or class 2, 2R or low-grade, or there was no cytology
- After hysterectomy or amputation of the cervix, if CIN3 was known to be present at the excision margin, and cytology was normal, benign, or class 2
- After cone biopsy, if CIN3 was known to be absent from the excision margin, and there was no cytology
- After cone biopsy, if it was not known whether CIN3 was present or absent from the excision margin or if CIN3 was known to be present at the excision margin, and cytology was normal, benign, or class 2
- After ring biopsy, if CIN3 was known to be absent from the excision margin, and there was no cytology
- After biopsy of unknown type, if CIN3 was known to be absent from the excision margin, and cytology was normal, benign, or class 2

Probably inadequate

- After hysterectomy or amputation of the cervix, if CIN3 was known to be present at the excision margin, and cytology was 2R or low-grade, or there was no cytology
- After cone biopsy, if CIN3 was known to be absent from the excision margin, and cytology was 2R or low-grade
- After cone biopsy, if it was not known whether CIN3 was present or absent from the excision margin or if CIN3 was known to be present at the excision margin, and cytology was 2R or low-grade, or there was no cytology
- After ring biopsy, if CIN3 was known to be absent from the excision margin, and cytology was 2R or low-grade
- After ring biopsy, if it was not known whether CIN3 was present or absent from the excision margin or if CIN3 was known to be present at the excision margin, and cytology was normal, benign or class 2, 2R or low-grade, or there was no cytology
- After punch or wedge biopsy, if cytology was normal, benign or class 2, 2R or low-grade, or there was no cytology
- After biopsy of unknown type, if CIN3 was known to be absent from the excision margin, and cytology was 2R or low-grade, or there was no cytology
- After biopsy of unknown type, if it was not known whether CIN3 was present or absent from the excision margin or if CIN3 was known to be present at the excision margin, and cytology was normal, benign or class 2, 2R or low-grade, or there was no cytology

Inadequate

- After any procedure, if cytology was class 3, 4, or 5, or high-grade

No cytology=no record that cytology had been done. *Classified either according to Papanicolaou or the modified Bethesda grading system;[9] cytology in the first 6 months after any procedure was excluded because reparative changes may give rise to false positive smears.[11] †Includes a small number of large loop excisions of the transformation zone. ‡Ring defined as a shallow cone biopsy <2 cm[12] or <1·5 cm deep[6] and not considered definitive treatment.[12] §Code used by the cytology laboratory at National Women's Hospital to show the presence of atypical cells suggestive of dysplasia (but less than carcinoma in situ) with the recommendation for a repeat smear.

	Adequate	Probably adequate	Probably inadequate	Inadequate
Women (N=1063)	299 (28)	294 (28)	196 (18)	274 (26)
Period of diagnosis				
1955–64	155 (40)	130 (34)	42 (11)	58 (15)
1965–74	61 (15)	80 (19)	111 (26)	170 (40)
1975–76	83 (32)	84 (33)	43 (17)	46 (18)
Age at diagnosis, years				
<30	61 (29)	51 (24)	41 (19)	61 (29)
30–39	127 (29)	128 (29)	81 (18)	104 (24)
40–49	81 (28)	79 (27)	49 (17)	81 (28)
≥50	30 (25)	36 (30)	25 (21)	28 (24)
Ethnicity				
Maori	17 (20)	19 (23)	21 (25)	27 (32)
European	269 (29)	263 (28)	167 (18)	237 (25)
Other or unknown	13 (30)	12 (28)	8 (19)	10 (23)
Parity				
Nulliparous	12 (19)	24 (37)	17 (26)	12 (19)
1–4	236 (29)	222 (27)	150 (18)	207 (25)
≥5	51 (28)	48 (26)	29 (16)	55 (30)
Maximum initial procedure				
Hysterectomy	100 (50)	94 (47)	1 (<1)	5 (3)
Cone biopsy	184 (31)	195 (33)	86 (14)	132 (22)
Ring biopsy	15 (14)	4 (4)	49 (45)	41 (38)
Punch or wedge biopsy	0	0	51 (36)	92 (64)
Unknown type of biopsy	0	1 (7)	9 (64)	4 (29)

Data are n and percentages.

Table 1: **Overall adequacy of treatment in the first 6 months after CIN3 diagnosis, by period of CIN3 diagnosis, age, ethnicity, parity, and maximum procedure within 6 months of diagnosis**

linkage); national death registers of New Zealand and Australia; and New Zealand electoral rolls current in 2002. The endpoint of the study was invasive cancer of the cervix (ICD-9 180) or vagina (ICD-9 184.0). Cancers were identified through medical records or linkage with cancer or death registers. For those cancers identified through medical records, the histopathology report was scrutinised by JB to decide whether sufficient detail was provided to meet current diagnostic standards; otherwise, the histopathology was reviewed.[5] Incident invasive cancers registered at a cancer registry were accepted.

Follow-up continued until death or Dec 31, 2000, whichever came first. The last date on which women were known to be alive (and free of cancer of the cervix or vagina) was before Dec 31, 2000, for 187 (18%) of the 1063 women in the final group who, for the purposes of our linkage with cancer and mortality data, were assumed to be alive and free of cancer on Dec 31, 2000. This assumption applied to 8·2% of woman-years at risk.

To identify clinically relevant groups of women and to account for procedures done during follow-up, every surgical procedure was classified according to the likelihood that the CIN3 lesion was completely removed. Treatment was defined as adequate, probably adequate, probably inadequate, or inadequate, depending on the type of procedure, presence of CIN3 at the excision margin, and subsequent cervical and vaginal cytology in the 6–24 months after the procedure (figure 1 and panel). Cytology in the first 6 months after any procedure was excluded because reparative changes can give rise to false-positive smears.[11] The severity of cytological abnormality was assessed according to the finding of the cytology review[9] for the first 2 years after diagnosis with CIN3; original cytology reports were used for later follow-up. Positive cytology comprised possible or definite high-grade lesions (modified Bethesda grading system) or class 3–5 smears (Papanicolaou system). The cytology laboratory at the National Women's Hospital originally used a code of "2R", with a recommendation for a repeat smear, to record the presence of atypical cells suggestive of dysplasia but less advanced than CIS (approximating to atypical squamous cells of uncertain significance [ASCUS] in Bethesda terminology or "borderline" in the British terminology). In this study, 2R smears were grouped with low-grade smears.

Any procedure followed by a positive smear in the following 6–24 months was classified as inadequate treatment (figure 1). Four women who developed cancer within 2 years of CIN3 diagnosis, but who had no follow-up cytology, were assumed to have had inadequate treatment. Initial treatment was defined as the most adequate procedure done within 6 months of CIN3 diagnosis.

The clinically relevant groups used in the analysis can be identified in figure 1 as follows: for the first aim (ie, estimation of the invasive potential of CIN3 by establishing the long-term risk of invasive cancer of the cervix or vaginal vault in women with cytological evidence of persisting disease within 2 years after initial treatment), group A comprised women with cytological evidence of persistent disease in the 6–24 months after initial treatment (figure 1, last row; n=[270+4 deemed to be inadequate]=274). For the second aim (ie, estimation of the long-term risk of invasive cancer of the cervix or vaginal vault in women who had minimum disturbance of their lesion [punch or wedge biopsy]), group B comprised women who had received initial treatment of a punch or wedge biopsy (figure 1, column headed "punch or wedge biopsy"; n=143). 92 women were in both group A and group B. For the third aim (ie, estimation of the long-term risk of cancer in women who received adequate treatment initially and conventional management thereafter, approximating current clinical practice), group C comprised women whose initial treatment was considered adequate or probably adequate (figure 1, n=[299+295–1 deemed to have inadequate treatment]=593).

The Auckland regional ethics committee gave approval for the present study, including approval for examination of medical records and formal review of cytological[9] and histopathological material.

Statistical analysis

In estimating the required cancer risks, we needed to account for treatments during follow-up. Assessment

of invasive potential of CIN3 (first two aims) needed an estimate of risk in women who, effectively, had no treatment. This estimate was approximated by use of women in group A (those with cytological evidence of persisting disease) and group B (those with minimum disturbance of the lesion), and censoring follow-up after a woman received a procedure classified as adequate or probably adequate. During the period of the clinical study and up to the time of the judicial review, treatment decisions were independent of perceived risk for many women so that censoring would often be uninformative (ie, unrelated to disease progress).

For the third aim, an estimate of risk was needed for women who received adequate (or probably adequate, see Results) initial treatment and conventional management during follow-up (group C). Because some women in this cohort received treatment that would not be considered appropriate by conventional standards, their follow-up was censored. Specifically, follow-up was censored if positive cytology was not followed within 6 months by a treatment of curative intent (cone biopsy, large loop excision of the transformation zone, loop electrosurgical excision procedure, amputation of the cervix or hysterectomy, or vaginectomy in women with positive vaginal smears after a hysterectomy).

Kaplan-Meier survival methods were used to estimate cumulative proportion of (first) cancer of the cervix or vaginal vault. 95% CIs were calculated by use of the log (–log of the survivor function).[13] Groups were compared by the log-rank test, and hazard ratios (HRs), designated here as relative risks (RRs) with their 95% CIs, estimated by use of Cox regression. A significance level of 0·05 (two-sided) was used throughout.

Role of the funding source

The Cancer Society of New Zealand, Wellington, New Zealand, provided funding, but had no role in study design, study implementation, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. MM and KS had access to the raw data. MM had full access to all of the data and the final responsibility to submit for publication.

Results

Between February, 2001, and April, 2002, medical records were reviewed for 1181 (96%) of the 1229 women; hospital staff could not locate the remaining 48 records. We excluded another 47 women, because there was no histopathology report for the initial diagnostic biopsy (n=3), the initial diagnosis of CIS was made outside the National Women's Hospital (n=34), diagnostic material had been removed from the National Women's Hospital (n=3), or there was a previous or concurrent diagnosis of invasive cancer of the cervix, vagina, or vulva (n=7). This left 1134 women (92% of 1229), some of whom had originally been diagnosed with CIS with microinvasion.

In the histopathological review, the diagnosis was cervical cancer for three (2%) of the 121 women in the random sample (each was stage 1A), 49 (21%) of the 231 women excluded by McIndoe and colleagues,[8] and 17 (49%) of 35 with an original report of possible microinvasion or invasion; additionally, two (<1%) of the 231 women excluded by McIndoe and colleagues had a lower grade CIN. These 71 women were excluded from further consideration, leaving a final group of 1063 women with CIN3, of whom 316 (30%) had their diagnosis confirmed by our histopathological review. In the blind histopathology review, 230 (97%) of 236 women

	All women, n	Women with cancer, n	Median follow-up, years (range)	Crude incidence per 100 000 woman-years (95% CI)	Percentage† (95%CI) of women with cancer of cervix or vaginal vault after:			
					5 years	10 years	20 years	30 years
Adequacy of initial treatment								
Inadequate‡	274	54	26·4 (0·3–42·2)	823 (630–1074)	8·5 (5·7–12·4)	12·6 (9·2–17·2)	18·4 (14·2–23·6)	20·7 (16·2–26·2)
Probably inadequate	196	7	27·9 (0·6–44·9)	132 (63–276)	0·5 (0·1–3·6)	2·1 (0·8–5·5)	3·2 (1·5–7·0)	4·0 (1·9–8·2)
Probably adequate	294	5	26·9 (1·6–45·0)	60 (25–144)	0·7 (0·2–2·7)	0·7 (0·2–2·7)	1·4 (0·5–3·8)	1·4 (0·5–3·8)
Adequate	299	4	27·8 (1·2–44·7)	46 (17–124)	0	0·3 (0·1–2·4)	1·5 (0·4–3·3)	1·5 (0·4–3·3)
Adequate+probably adequate§	593	9	27·4 (1·2–45·0)	53 (28–102)	0·3 (0·1–1·4)	0·5 (0·2–1·6)	1·4 (0·7–2·9)	1·4 (0·7–2·9)
Maximum initial procedure								
Hysterectomy	200	3	31·0 (1·2–45·0)	51 (17–159)	0·5 (0·1–3·5)	1·0 (0·3–4·0)	1·6 (0·5–5·0)	1·6 (0·5–5·0)
Cone biopsy	597	21	26·2 (0·8–42·5)	127 (83–195)	1·0 (0·5–2·2)	1·2 (0·6–2·5)	3·2 (2·0–5·0)	3·6 (2·3–5·6)
Ring biopsy	109	10	26·8 (0·6–44·9)	360 (194–670)	0·9 (0·1–6·5)	5·7 (2·6–12·2)	8·6 (4·6–15·9)	10·2 (5·6–18·4)
Punch or wedge biopsy¶	143	34	28·0 (0·3–42·3)	1023 (731–1432)	11·3 (7·1–17·8)	17·0 (11·8–24·3)	22·2 (16·2–30·1)	24·6 (18·2–32·6)
Unknown type of biopsy	14	2	27·6 (1·2–43·1)	550 (138–2200)	14·3 (3·8–46·1)	14·3 (3·8–46·1)	14·3 (3·8–46·1)	14·3 (3·8–46·1)
Inadequate initial treatment and punch or wedge biopsy only‖	92	34	26·5 (0·3–40·7)	1731 (1237–2422)	17·4 (11·1–26·9)	26·2 (18·4–36·5)	34·0 (25·2–44·7)	37·5 (28·4–48·3)

*No account has been taken of treatment during follow-up. †Kaplan-Meier estimate. ‡Group A. §Group C. ¶Group B. ‖Subset of group A and of group B.

Table 2: **Incidence of cancer of the cervix or vaginal vault by adequacy of initial treatment and extent of initial procedure***

	All women, n (n=274)	Women with cancer, n (n=47)	Unadjusted relative risk*	Adjusted relative risk† (95% CI)	p
Age at CIN3 diagnosis					
<30	61	8	1·0	1·0	..
30–39	104	11	0·8	0·6 (0·2–1·5)	0·2
40–49	81	17	1·8	1·2 (0·5–2·9)	0·6
≥50	28	11	3·7	2·5 (1·0–6·7)	0·06
Ethnicity					
Maori	27	6	1·3	0·7 (0·3–1·9)	0·5
European	237	39	1·0	1·0	..
Other or unknown	10	2	0·9	1·2 (0·3–5·2)	0·8
Parity					
Nulliparous	12	3	1·7	1·5 (0·5–5·3)	0·4
1–4	207	29	1·0	1·0	..
≥5	55	15	2·2	2·5 (1·2–5·1)	0·01
Period of CIN3 diagnosis					
1955–64	58	6	1·0	1·0	..
1965–74	170	39	2·8	1·1 (0·3–3·8)	0·9
1975–76	46	2	0·5	0·6 (0·1–3·0)	0·5
Maximum initial procedure					
Cone biopsy	132	9	1·0	1·0	..
Ring biopsy	41	5	1·8	1·4 (0·4–4·5)	0·5
Punch or wedge biopsy	92	31	5·1	4·6 (1·7–12·0)	0·002
Other	9	2	3·2	1·6 (0·3–9·8)	0·3

*Hazard ratio, calculated by use of Cox regression. †Adjusted for all other variables using the categories shown.

***Table 3*: Risk of invasive cancer of the cervix or vaginal vault in women with persistent CIN3 after initial treatment, by age, ethnicity, parity, period of CIN3 diagnosis, and maximum initial procedure**

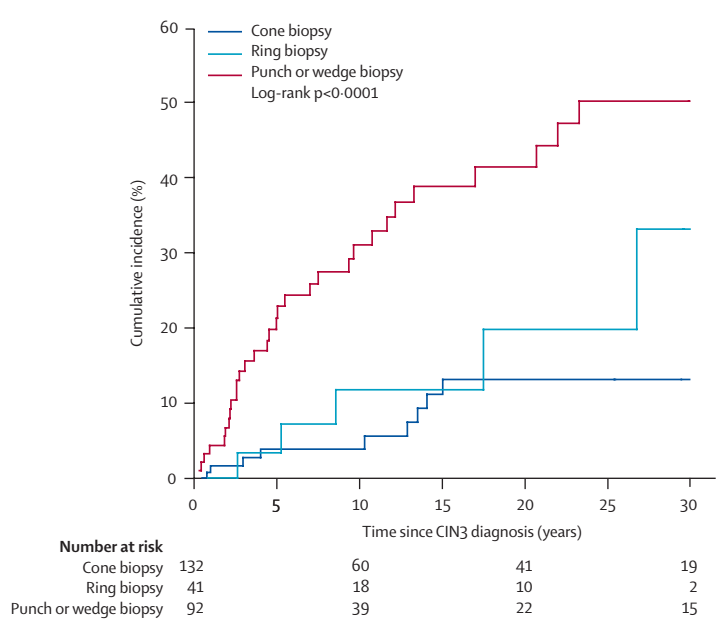

***Figure 2*: Cumulative incidence of cancer of the cervix or vaginal vault in women with cytological evidence of persistent disease after initial treatment according to whether their maximum initial procedure was a cone biopsy, a ring biopsy, or a punch or wedge biopsy**

with an original diagnosis of CIS were found to have CIN3.

Median age at diagnosis of CIN3 was 38 years (range 21–74) in the 422 women diagnosed during the main period of the clinical study in 1965–74, 38 years (16–64) in the 385 women diagnosed in 1955–64, and 32 years (19–72) in the 256 women diagnosed in 1975–76. Hysterectomy was a common initial treatment in the diagnostic period 1955–64 (138 of 385 women [36%]), but not in 1965–74 (37 of 422 women [9%]) or in 1975–76 (25 of 256 women [10%]). Cone biopsy was the initial treatment in a higher proportion of women diagnosed in 1955–64 (226 of 385 [59%]) and in 1975–76 (193 of 256 [75%]) than in 1965–74 (178 of 422 [42%]). For women diagnosed in 1965–74, the maximum initial treatment was ring biopsy (72 of 422 [17%]) or punch or wedge biopsy (127 of 422 [30%]), which were rarely used in 1955–64 (ring: 15 of 385 [4%]; punch or wedge: two of 385 [<1%]) or 1975–76 (ring: 22 of 256 [9%]; punch or wedge: 14 of 256 [5%]).

Of the 1063 women, 593 (56%) received treatment classified as adequate or probably adequate within 6 months of their diagnosis with CIN3, whereas for 274 (26%) women the treatment was defined as inadequate due to positive cytology within 6–24 months (table 1). A far higher proportion of women had inadequate or probably inadequate treatment during the main period of the clinical study (1965–74) compared with the other two time periods, but there were no clear patterns in treatment adequacy by age or parity. That relatively more Maori women had inadequate or probably inadequate treatment compared with non-Maori women (table 1) was consistent with the higher proportion of Maori who were diagnosed during 1965–74 (data not shown).

Of the 1063 women, 70 developed cancer of the cervix or vagina during follow-up (median 27·1 years after diagnosis of CIN3, range 0·3–45·0). All 13 vaginal cancers were in the vault; three of the 70 women had cancer at both sites. 54 of the cancers occurred in the group who received inadequate treatment initially, in whom the crude cancer incidence was more than ten-times that in women whose initial treatment was adequate or probably adequate (table 2). As risks were similar in women with adequate and probably adequate initial treatment, these two groups were combined for further analyses. The crude incidence in the combined group (group C) was 53 (95% CI 28–102) per 100 000 woman-years.

Further categorisation according to the maximum initial procedure showed the risk was highest in the group of women who had at most a punch or wedge biopsy and whose treatment was classified as inadequate (due to evidence of persisting positive cytology) (table 2). By 30 years after diagnosis 37·5% of the women in this group had developed invasive cancer. The crude estimates of risk (that is, without censoring) shown in table 2 cannot be applied to any relevant current clinical populations because of variation in management after initial treatment, such as the withholding of treatment of

	All women, n	Women with cancer, n	Median follow-up, years (range)	Crude incidence per 100 000 woman-years (95% CI)	Percentage* (95% CI) of women with cancer of cervix or vaginal vault after:			
					5 years	10 years	20 years	30 years
Minimum disturbance of CIN3 lesion (initial treatment by punch or wedge biopsy—group B)†								
(i) All women irrespective of cytology in 6–24 months after initial treatment	143	31	10·8 (0·3–42·3)	1535 (1080–2183)	13·0 (8·2–20·4)	20·0 (13·7–28·7)	26·1 (18·6–35·9)	31·3 (22·7–42·3)
(ii) Subset with persistent disease in 6–24 months after initial treatment‡	92§	31	7·6 (0·3–40·7)	2887 (2030–4105)	19·9 (12·6–30·5)	31·1 (21·7–43·4)	41·5 (30·2–55·0)	50·3 (37·3–64·9)
Initial treatment categorised as adequate or probably adequate (group C)								
With censoring for inappropriate subsequent treatment¶	593	5	26·8 (1·2–45·0)	30 (13–72)	0·3 (0·1–1·4)	0·3 (0·1–1·4)	0·7 (0·3–1·9)	0·7 (0·3–1·9)

*Kaplan-Meier estimate. †Follow-up censored after any procedure classified as adequate or probably adequate treatment. ‡This is identical to the subset derived from women with persistent disease 6–24 months after initial treatment (group A) when restricted to those with initial treatment no more extensive than punch or wedge biopsy. §Two additional women were deemed to have persistent disease. ¶Follow-up censored if positive cytology was not followed within 6 months by a treatment of curative intent.

Table 4: **Proportions of women developing cancer of the cervix or vaginal vault in those with minimum disturbance of the CIN3 lesion (group B) and in those with adequate or probably adequate initial treatment (group C)**

curative intent from some women. This variation in management has been taken into account in the remainder of the Results section by censoring as described in the Methods section.

For the first aim, the long-term risk of invasive cancer of the cervix or vaginal vault was estimated in 274 women with evidence of persistent CIN3 after initial treatment (ie, with positive cytology 6–24 months after their initial management; group A) in table 3. Follow-up was censored for 139 (51%) of the 274 women when they received subsequent treatment classified as adequate or probably adequate; censoring was within the first 10 years for 115 (83%) of the 139 women. During follow-up, 47 women were diagnosed with cancer, and seven more cancers were diagnosed in women who had been censored. Cancer risk was raised in women with five or more children. After adjustment for demographic characteristics and the maximum extent of the initial procedure (ie, cone, ring, or punch or wedge biopsy, or other procedure), RR for 1965–74 decreased from 2·8 (unadjusted) to 1·1 (table 3). On the information available from 151 of the cone and ring biopsies in the random blind histopathology review, there was no clear evidence that the size of the CIN3 lesion (a known prognostic factor[14]) differed by period of diagnosis, the median area being about 200 mm² (range 8–992).

However, cancer risk did vary according to the maximum extent of the initial procedure, with women who had a punch or wedge biopsy having 4·6-times the risk of those having a cone biopsy (p=0·002, table 3 and figure 2). Of women with persistent disease whose initial maximum treatment was a cone biopsy, 3·4% (95% CI 1·5–10·3%) had developed cancer by 10 years and 13·2% (6·6–24·5) by 30 years, whereas of those whose initial management was a punch or wedge biopsy, 31·1% (21·7–43·3) had developed cancer by 10 years and 50·3% (37·3–64·9) by 30 years. To rule out an undetected residual period effect due to changes in size of lesion and in diagnostic and treatment techniques, a re-analysis restricted to women diagnosed in the main

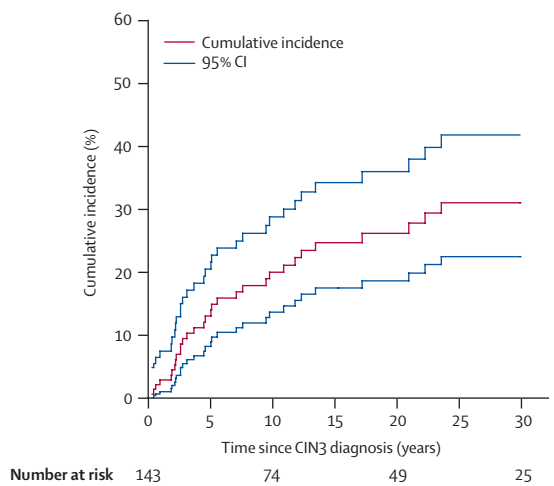

Figure 3: **Cumulative incidence of cancer of the cervix or vaginal vault in women with minimum disturbance of the CIN3 lesion (no more than a punch or wedge biopsy)**

period of the clinical study (1965–74) was done with similar findings (data not shown).

The long-term risk of invasive cancer of the cervix or vaginal vault in women with minimum disturbance of their lesion was estimated by following up the 143 women who had an initial procedure no more extensive than punch (n=115 [80%]) or wedge (n=28 [20%]) biopsy (group B). Of the 143 women, 127 (89%) had been diagnosed with CIN3 in 1965–74, two (1%) in 1955–64, and 14 (10%) in 1975–76. Follow-up was censored at the time of subsequent adequate or probably adequate treatment for 62 (43%) of the 143 women, and within the first 10 years for 43 (69%) of these 62 women. Three cancers were diagnosed in women who had been censored, leaving 31 cancers in the follow-up period. Of the 143 women, 19 (13%) had no follow-up cytology within

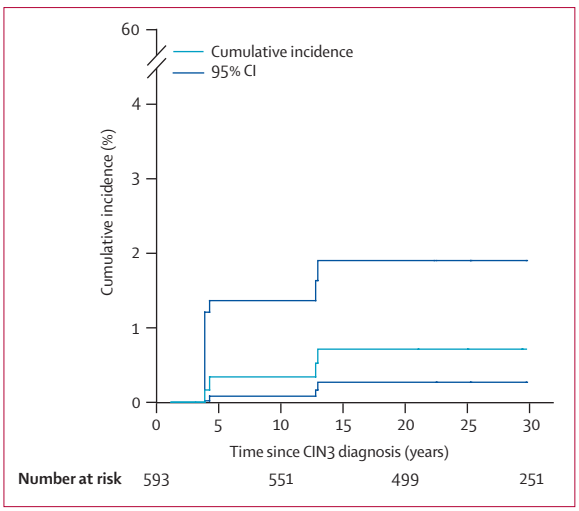

Figure 4: **Cumulative incidence of cancer of the cervix or vaginal vault in women with initial treatment classified as adequate or probably adequate and conventional management thereafter**

6–24 months after initial management, 24 (17%) had normal or benign cytology, ten (7%) had low-grade abnormalities, and the remaining 90 (63%) had cytological evidence of persistent disease. All 31 cancers occurred in women diagnosed with CIN3 in 1965–74 and who had persistent disease. In all 143 women, the cumulative percentage for cancer of the cervix or vaginal vault was 20·0% (95% CI 13·7–28·7) by 10 years and 31·3% (22·7–42·3) by 30 years (table 4, figure 3). There was no evidence of variation in risk by age, ethnicity, or parity (data not shown). As described above, in the 92 women with both minimum disturbance of their lesion and persistent disease, the risk was 31·1% (21·7–43·4) by 10 years and 50·3% (37·3–64·9) by 30 years (table 4).

These findings can be compared with the long-term risk of invasive cancer of the cervix or vaginal vault in the 593 women who received adequate or probably adequate treatment initially and conventional management thereafter (group C). Of these 593 women, 285 (48%) had been diagnosed with CIN3 in 1955–64, 141 (24%) in 1965–74, and 167 (28%) in 1975–76 (table 1). To take into account subsequent treatment that did not meet our definition of "conventional", follow-up was censored in 16 (3%) women in whom a positive smear was not treated according to the censoring criteria. Of the nine cancers, four (two cervix, two vaginal vault) occurred in these 16 women after their follow-up was censored. This left five cancers (four cervix, one vaginal vault) in the follow-up period, the median duration being 26·8 years (range 1·2–45·0). The cumulative percentage of women with cervical or vaginal vault cancer was 0·3% (95% CI 0·1–1·4) by 10 years and 0·7% (0·3–1·9) by 30 years (table 4, figure 4). One further cancer occurred at 32 years. The standardised incidence ratio (SIR) for cancer of the cervix or vaginal vault in women who received adequate or probably adequate treatment and conventional management thereafter (based on age-specific and period-specific rates for the New Zealand population) was 1·3 (0·4–3·1).

Discussion

Our analysis provides the most direct estimates yet available of the rate of progression from CIN3 to invasive cancer. In women who had minimum disturbance of their lesion (punch or wedge biopsy) initially and no subsequent adequate treatment, 31% developed cancer within 30 years. This probably underestimates the true invasive potential of CIN3, because even a small diagnostic biopsy might be curative for some women.[15] If we focus on the subset of this group who had persistent disease after their biopsy (as identified by positive cytology within 6–24 months), 50% of the women developed cancer within 30 years. This approach might overestimate the invasive potential, because it ignores the possibility of spontaneous regression within the first 24 months. Therefore, the true number will be between these two extremes.

By contrast is the prognosis for women treated conventionally. In this group, the risk of cancer of the cervix or vaginal vault was only 0·7% after 30 years. Our criteria meant that none of these women had persistent CIN3 in the period 6–24 months after their initial treatment, but similar findings could be achieved today with close monitoring, since women with persistent or recurrent disease after initial treatment normally would receive further treatment without delay.

Our estimates are based on data for women of whom many were not adequately treated although all were assiduously followed up, providing numerous smears for assessment of the adequacy of treatment. The quality of the data was augmented by the high proportion of original material retrieved for histopathology and cytology, and by the existence of clinic records that contained information about cytology and gynaecological procedures done outside the National Women's Hospital.

In early studies of biopsy-proven but untreated CIS, the proportion that progressed to invasive cancer ranged from 24% to 75%.[16] Modelling approaches have been used to estimate the lifetime risk of cervical cancer in women with untreated CIN3 as 15–23% in Sweden[17] and 40% (about 1% annually) in England and Wales.[18] Our estimate of 31% at 30 years is close to the estimate for England and Wales.

Although McIndoe and colleagues published an analysis of data from nearly the same women as group A in our study, somewhat different inclusion and exclusion criteria were used, follow-up continued only until 1983, no account was taken of the type of initial treatment, and there was no censoring for subsequent adequate treatment.[8] In their analysis, with groups based solely on cytological follow-up, cancer of the cervix or vaginal vault developed in 18% of women with persistent positive cytology by 10 years and 36% by 20 years. The comparable numbers from the present study are 16% of women by 10 years and 25% by 20 years in all women with persistent disease, irrespective of initial treatment but censoring for subsequent adequate

or probably adequate treatment (data not shown). The lower risk in our analysis is mainly attributable to our definition of inadequate treatment as at least one high-grade smear within 6–24 months of initial treatment, whereas McIndoe and colleagues included only women whose smears repeatedly showed high-grade abnormalities. In our study, false-positive smears were unlikely in the 6–24 months after diagnosis of CIN3 because smears less than 6 months after any procedure were excluded, all cytology in the first 24 months was reviewed (4930 of 5478 [90%] smears were available, 4477 of 4930 [91%] of those available were technically satisfactory), and the cytology review showed good agreement between original and review coding.[9] Therefore, a single positive smear in the 6–24 months after the initial procedure suggested a high probability of persistent disease. The higher risk recorded in the McIndoe analysis suggests that the repeated finding of high-grade cytological abnormality identified CIN3 that was more likely to progress to cancer. Without censoring, our estimates of risk were even lower (12·6% after 10 years and 18·4% after 30 years, table 2).

When type of initial treatment was taken into account in our analysis, the risk of invasive cancer in women with persistent disease (group A) was substantially lower after cone biopsy than after punch or wedge biopsy. This finding could be due to the smaller extent of residual CIN3 after cone biopsy. An alternative explanation is that cancer risk in women with persistent disease depends on whether the tissue at greatest risk, namely the transformation zone, has been removed entirely.[19] Consequently, estimates of the invasive potential of CIN3 are misleading unless type of initial treatment is taken into account.

There are five published reports of cohorts of women with treated CIN3 in whom subsequent cancers were ascertained through linkage with a cancer registry.[20–24] In three of these series reanalysed by Soutter and colleagues,[25] the rate of invasive cancer was 53 per 100 000 woman-years (cervix only) in Sweden,[20] 48 per 100 000 woman-years (cervix or vagina) in England,[21] and 86–194 per 100 000 woman-years (cervix or vagina) in Northern Ireland.[22] In an extension of the Swedish study, the incidence of invasive cancer was estimated to be 43 per 100 000 woman-years (cervix or vagina) with an SIR for cervical cancer of 2·3 (95% CI 2·2–2·5) and for vaginal cancer of 6·8 (5·6–8·2).[23] The SIR for cervical cancer in Finland was 2·2 (0·5–6·4, based on three women with cancer).[24] In none of these studies could subsequent treatment be taken into account. Our estimate of 30 (13–72) per 100 000 woman-years (table 4) and SIR of 1·3 (0·4–3·1) are not directly comparable to the above. The incidence will be lower than the estimates for other treated cohorts because most of the women remained under close clinical surveillance and absence of treatment after a positive smear was taken into account in our analysis by censoring. Furthermore, in our cohort a high percentage of women received a hysterectomy either initially (n=194, 33%) or during follow-up (n=95, 16%). The estimate of 53 (28–102) per 100 000 woman-years from our uncensored analysis (table 2) also is not comparable because of the planned unconventional management of a small number of women during follow-up.

Three sources of bias could have led us to underestimate the invasive potential of CIN3 in women with persistent disease and in those with minimum disturbance of the lesion. Firstly, our analysis assumes that, had they not been treated, censored women would have had the same cancer risk as those not censored. However, subsequent treatment might have been given more often to women perceived to be at higher risk. Secondly, as censoring occurred only when subsequent treatment was considered to be adequate or probably adequate, some women would have remained in the analysis following an extensive procedure when there was no information about disease at the excision margin or follow-up cytology. Thirdly, as records of clinical follow-up became less complete during the late 1980s and the 1990s, some women might have had unrecorded treatment during later follow-up.

As the blind histopathology review detected three (2%) stage 1A cancers in 121 women whose original diagnosis was CIS, there might have been about 15 stage 1A cancers in the 747 women whose histopathology was not subject to review. However, we can assume that these 15 cases would be distributed proportionately according to initial management. When the initial treatment was a cone biopsy or hysterectomy, any stage 1A cancer would probably have been removed, but not in the 143 women whose initial treatment was a punch or wedge biopsy. Of these 143 women, the histopathology was reviewed in all but 93, in whom two stage 1A cancers might have been expected; one was diagnosed in this unreviewed group within 24 months of CIN3 diagnosis.

Whereas CIN3 comprises severe dysplasia and CIS, an unpublished review of histopathology records suggested that the diagnosis of severe dysplasia was rarely used at the National Women's Hospital during the period of the clinical study. Because organised cervical screening programmes had not been introduced at the time of the clinical study, the women tended to be older, their CIN3 would have been diagnosed later, and consequently, with larger lesions than is common in developed countries today.[26] For these reasons, our findings might be more applicable to a previously unscreened cohort of women. There are no population-based data on CIN3 incidence or age distribution in New Zealand for the period of this study.

Of note, the judicial inquiry acknowledged the obligation to offer treatment and counselling to women whose management had been inadequate. The medical advisers to the inquiry assessed the clinical records of all women and identified 69 for whom concern remained. These women were notified to the Ministry of Health who arranged independent clinical review for all women who had not received adequate management in the interim.[4,7]

Although human papillomavirus (HPV) infection is a necessary cause of CIN3 and cervical cancer,[27] various

cofactors, including high parity, long-term oral contraception, and tobacco smoking, seem to modify the risk of progression from HPV infection to CIN3 and cervical cancer.[28] High parity was associated with an increased risk in this study, but the medical records held insufficient data to assess any effects of smoking or oral contraception. Archival diagnostic material from 162 of these women with CIN3 was tested previously for the presence of HPV-6, HPV-11, HPV-16, and HPV-18 DNA sequences. No difference in virological profile was noted between 81 women who did, and 81 who did not, have persistent disease 24 months after diagnosis.[29]

In conclusion, our study was made possible by the existence of an unethical clinical study many years ago, in which treatment was often withheld or delayed. The findings show that untreated CIN3 has a considerable propensity to progress to invasive cancer, whereas the risk is very low in women treated conventionally throughout.

Contributors

All co-authors contributed to the analysis and interpretation of data, and approved the final version of the report. RJ, DS, CP, MM, JB, and KS conceived and designed the study. MM and RJ supervised the study. JB did the histopathology review. GM supervised and participated in the cytology review. KS did the statistical analyses. MM drafted the manuscript and all authors contributed to its development and revision.

Conflicts of interest

CP was a medical adviser to the judicial inquiry into the treatment of women with cervical carcinoma in situ at National Women's Hospital.[4] All other authors declared no conflicts of interest.

Acknowledgments

We are grateful to the Cancer Society of New Zealand for funding; Medical Records staff at the National Women's Hospital for locating medical records; Penny Lewis, and Bernadette McEwan for abstracting data from medical records; Anna Davies (New Zealand Health Information Service—New Zealand Cancer Registry and New Zealand National Mortality Database), Diane Skilton (Queensland Department of Health—Queensland Cancer Registry), Elizabeth Tracey and Rajah Supramaniam (New South Wales Cancer Council—New South Wales Central Cancer Registry), John Harding (Australian Institute of Health and Welfare—Australian National Death Index), for arranging or undertaking (or both) linkage with the relevant databases; Brian Clarke (New Zealand Department of Internal Affairs—Registry of Births, Deaths and Marriages), for approving the manual search of death records; Michael Churchouse, for extracting archived cytology and histology material from storage; Brian Cox (Hugh Adam Cancer Epidemiology Unit), for age-specific and period-specific cancer incidence rates for New Zealand; and the women who were the focus of the New Zealand Cervical Cancer Inquiry.

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