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The Invasive Potential of Carcinoma In Situ of the Cervix

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Nine hundred and forty-eight patients with carcinoma in situ (CIS) of the cervix diagnosed histologically have been followed from five to 28 years. Among the 817 patients who had normal cytology follow-up, 12 (1.5%) developed invasive carcinoma. A second group of 131 patients continued to produce abnormal cytology consistent with cervical neoplasia, and 29 (22%) of them developed invasive carcinoma of the cervix or vaginal vault. Patients with continuing abnormal cytology after initial management of CIS of the cervix are 24.8 times more likely to develop invasive carcinoma than women who have normal follow-up cytology. Further, when compared with the population at large, the chances of patients with normal follow-up cytology developing invasive cervical or vaginal vault carcinoma increase 3.2-fold over women who have never had CIS of the cervix. ***(Obstet Gynecol 64:451, 1984)***

It is now generally accepted that carcinoma in situ (CIS) of the cervix has a significant invasive potential. In this paper, the authors report the results of a long-term follow-up study of patients with an initial diagnosis of CIS of the cervix, some of whom subsequently developed invasive carcinoma of the cervix or vaginal vault. This study has been in progress at the National Women's Hospital, Auckland, New Zealand, since 1955.

There have been differences of opinion within the hospital on the invasive potential of CIS of the cervix. Earlier National Women's Hospital experience pointed to CIS having an insignificant invasive potential.[1] In 1966 the senior medical staff agreed to a study of patients whose only abnormal finding was positive cervical cytology. No further treatment was to be offered to a group of patients who had no clinical, cytologic, or colposcopic evidence of invasive carcinoma, and in whom the histologic diagnosis of CIS of the cervix had been established by a limited biopsy of the most significant area.[1] The object was to study the natural history of CIS of the cervix after a representative biopsy with minimal disturbance of the lesion. This conservative approach was also extended to include some other women in whom abnormal cytology continued after initial treatment. It is stressed that only a proportion of women in the present study were managed in this manner. The remaining patients with abnormal cytology were managed by conventional techniques.

The conclusions of this paper on the invasive potential of CIS of the cervix are based on a comparison of two groups of women after an initial diagnosis of CIS: In one group the follow-up cytology was normal and in the other it was abnormal. The authors infer the presence of persisting abnormal cytology, after an initial diagnosis of CIS, as indicating the presence of continuing neoplasia in the lower genital tract. A comparison is also made of the incidence of invasive carcinoma of the cervix between the group with normal cytology follow-up and the New Zealand population at large.

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Table 1. Definitive Management of 948 Women

Cone biopsy and amputation cervix		
Punch and/or wedge biopsy, later cone biopsy	184	
Cone biopsy	483	
Amputation cervix	6	
Subtotal		673
Total hysterectomy		
Punch and/or wedge biopsy, later TH	38	
Cone biopsy, later TH	185	
Primary TH	27	
Subtotal		250
Other		
Outpatient punch biopsy only	11	
Punch, later wedge biopsy	7	
Wedge biopsy only	7	
Subtotal		25
Total		948

TH = total hysterectomy.

Materials and Methods

The present study reviews all of the 1028 women diagnosed histologically as having CIS of the cervix between January 1955 and December 1976 and who, except for one patient, have since been followed for a minimum of five years. Nine hundred ninety-five of these women were initially identified by abnormal cervical cytology, and in 33 cases the diagnosis was a chance histologic finding.

Eighty patients (7.8%) have been excluded from the study. Of these, 29 patients (2.8%) were lost to follow-up. Thirteen women died of intercurrent disease within five years. Eight patients developed invasive cervical carcinoma within one year of the initial biopsy. This 12-month interval has been allowed to avoid the possibility that invasive carcinoma had been missed at the initial biopsy. Thirty patients with continuing abnormal cytology after the diagnosis of CIS, but in whom a final histologic diagnosis had not been made (at review date June 1983), have also been excluded from the study. The authors assume these women have continuing CIS but, without a further biopsy, this cannot be confirmed. Thus, 948 patients were available for the present study.

Policy within the hospital for the management of patients with CIS has varied. In the early years, the majority of clinicians used a cone biopsy as the initial management of women presenting with abnormal cervical cytology. Since 1964, colposcopically directed punch biopsy has been used as an initial biopsy procedure in an increasing proportion of cases, usually followed by cone biopsy. Twenty-five cases had only a colposcopically directed punch or wedge biopsy. The few clinicians who initially performed punch or wedge biopsy alone had abandoned the practice by 1970.

The definitive management of the 948 patients is summarized in Table 1. In 673 patients, cone biopsy (667) or amputation of the cervix (6) were the principal mode of management, preceded by punch or wedge biopsy in 184 patients, and cone biopsy alone in 483 women. In 250 patients, management was by total hysterectomy, preceded by punch and/or wedge biopsy in 38 patients and by cone biopsy alone in 185. In 27 patients, hysterectomy was the primary procedure, CIS being an unexpected finding in the excised specimen. Only nine of the 250 hysterectomies were performed by the vaginal route. The only biopsies in 25 women were punch biopsy in 11, wedge biopsy preceded by punch biopsy in seven, and wedge biopsy alone in seven.

Patients were followed with clinical and cytologic examinations three and six months after the initial biopsy and thereafter at yearly intervals from five to 28 years or the development of invasion (Table 2). Colposcopy and/or repeat biopsy procedures were performed if the clinician responsible for the case believed that such techniques would be helpful in further management. Many patients had multiple biopsies (Figures 1, 2, and 3). Some patients had equivocal follow-up cytology findings during the first two years after the initial biopsy, but by the end of this period, cytology was consistently normal or abnormal.

Follow-up cytology was used as the basis for the division of the patients into two groups. Group 1 consisted of patients with normal cytology follow-up after two years, whereas group 2 patients had persistent equivocal or abnormal cytology follow-up findings at that time.

One of the authors (MRM) supervised the diagnosis of all cervical histopathology. Immediately after excision, cervical cone biopsies were routinely opened at the three o'clock position by the surgeon. After fixation in 10% formal saline, the cones were oriented and cut serially into blocks 3 mm thick. After processing, at least three step serial sections were cut from each block and stained with hematoxylin and eosin. An average of 40 step serial sections were taken from each cone

Table 2. Follow-Up of All Patients to Review Date (June 1983) or to Development of Invasion

Years	Group 1	Group 2	Total
4	4	11	15
5–9	295	37	332
10–14	136	52	188
15–19	202	26	228
20–24	137	5	142
25 +	43		43
Total	817	131	948

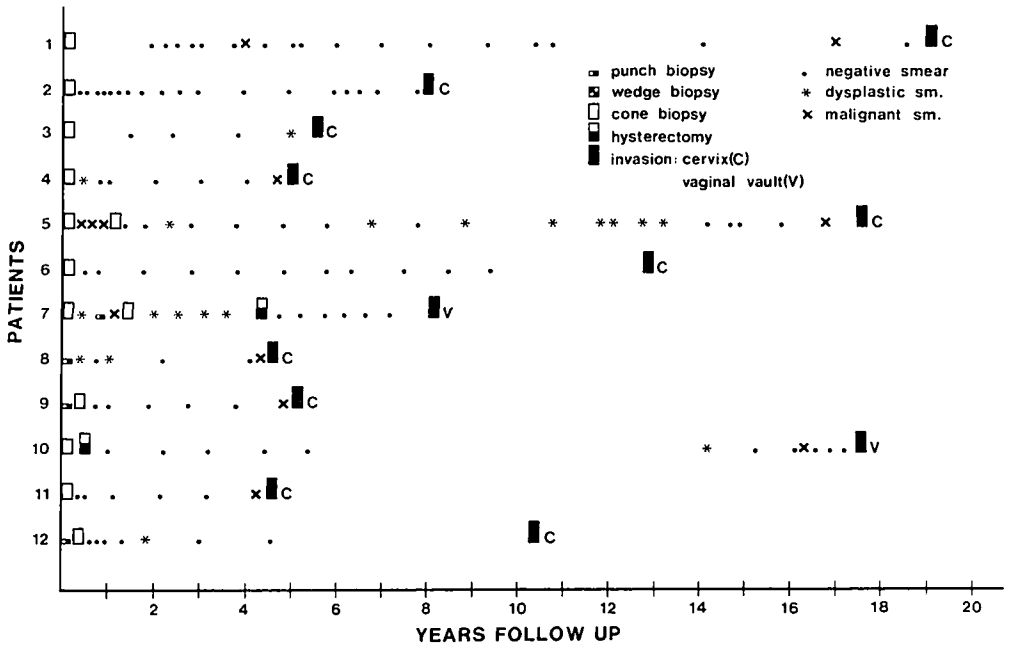

Figure 1. Follow-up details to invasion of 12 women among 817 group 1 patients who developed invasive carcinoma; ten cervix and two vaginal vault after earlier hysterectomy.

biopsy specimen. Smaller biopsies were dealt with similarly. Hysterectomy specimens were immediately opened anteriorly and, after fixation, the cervix was oriented, completely blocked, and dealt with in a manner similar to that for cone biopsy.

The authors' histologic criteria for CIS were those described by Reagan and Hicks.[2] Carcinoma in situ was morphologically and cytologically similar to invasive carcinoma but lacked the feature of invasion. It may show the variation of microscopic appearances seen in invasive carcinoma ranging from differentiated to undifferentiated carcinoma. Every effort was made to maintain uniform histologic criteria. Because the authors included what many call severe dysplasia in their numbers for CIS, their histologic criteria for CIS were similar to those described by Richart[3] for cervical intraepithelial neoplasia grade 3 (CIN 3). Patients with microinvasive carcinoma (FIGO 1976 stage Ia) and occult invasive carcinoma (stage Ib occ) were excluded from this study.

The Cox regression model[4] was used to analyze the data. The intervals from diagnosis to invasion in the two groups were compared, and a graphic representation was produced based on the Kaplan and Meier[5] estimates of survival (Figure 4). The incidence of invasion was analyzed using the method of Mantel and Haenszel.[6]

Results

The ages of patients at the time of initial diagnosis ranged from 17 to 77 years (median 37). The descriptive data of the two groups are summarized in Table 3. Of note are the differences in proportion of noncaucasian and median age at diagnosis. These variables, as well as parity, were included in a Cox regression analysis of the data to counter any effect these differences might have.

The figures in Table 2 reflect follow-up to review date June 1983 (and include earlier death from intercurrent disease) or to invasion. This table does not include follow-up information after the development of invasion, explaining the shorter follow-up time in group 2 patients. One patient (case 49, Figure 3) progressed from initial diagnosis of CIS to invasion and subsequently died within three years, and so did not complete the minimum five years allowed for follow-up.

The 817 patients in group 1 remained clinically and cytologically normal for the first four years after the initial biopsy, irrespective of whether or not there was evidence of complete excision of CIS. They were managed as outlined in Table 4. The principal management was by cone biopsy in 579 patients, amputation of the cervix in six, total hysterectomy in 217, outpatient punch biopsy alone in six, wedge biopsy preceded by outpatient punch biopsy in four, and wedge biopsy alone in five. In the 579 cone biopsy cases, excision was histologically incomplete in 139 (24%). Excision was also histologically incomplete in the 15 cases of punch or wedge biopsy, but was complete in the six cases in which the cervix was amputated. Two of the 217 total hysterectomy specimens showed CIS at the vaginal cuff excision margins.

In this first group of 817 patients with normal follow-up cytology, 799 (97.8%) showed no cytologic or clinical evidence of recurrence of CIS or the development of

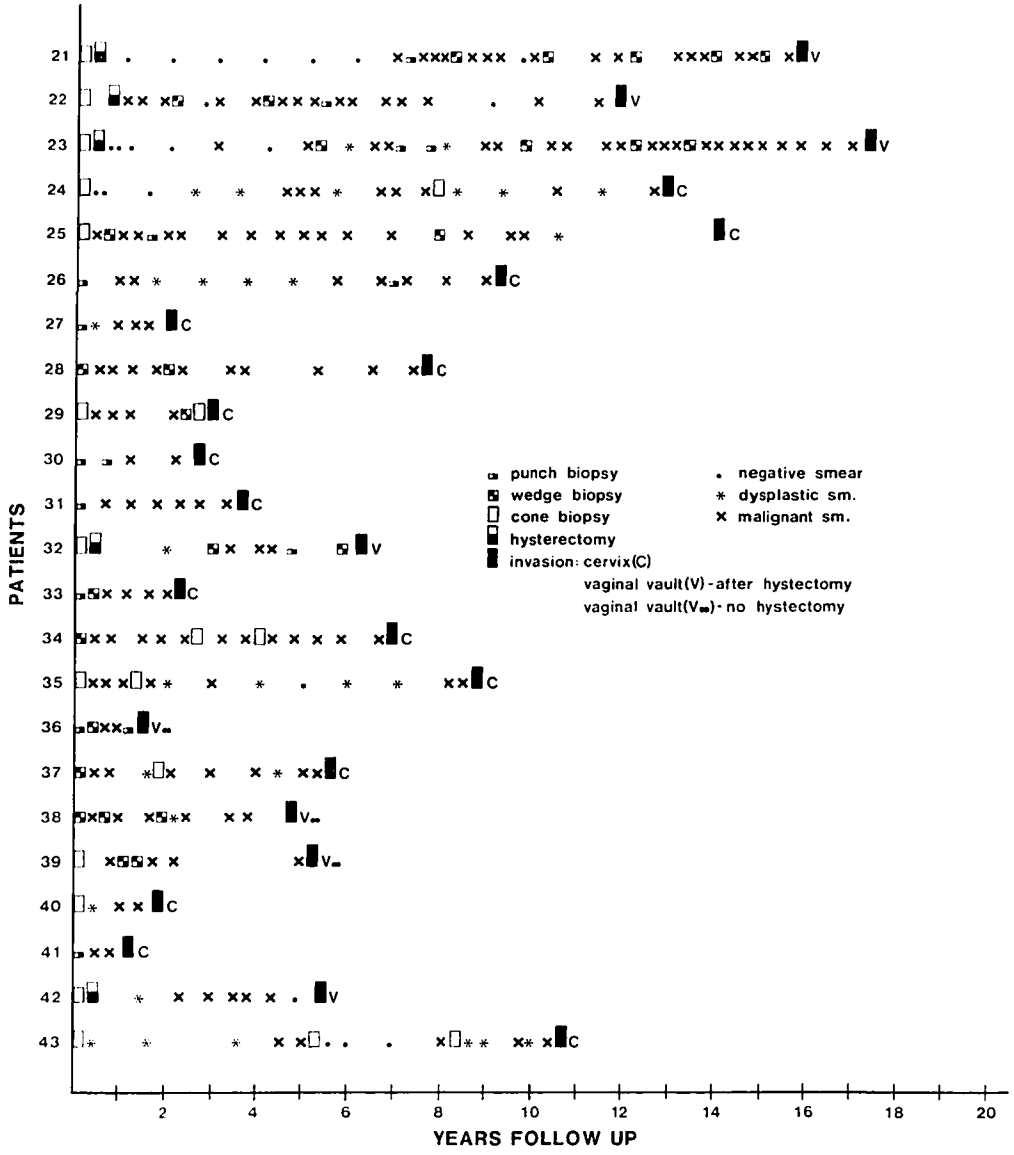

Figure 2. Follow-up details to invasion of 23 women among 131 group 2 patients with good follow-up, who developed invasive carcinoma; 15 cervix and eight vaginal vault.

invasive carcinoma when followed from five to 28 years. Of the remaining 18 women, 12 (1.5%) developed invasive carcinoma four to 19 (median nine) years later—of the cervix in ten, and of the vaginal vault in two (Table 5). Carcinoma in situ recurred in six (0.8%) patients four to 11 (median 6.5) years after the initial cervical biopsy. Of the 12 group 1 patients who developed invasive carcinoma, nine followed cone biopsy, two followed hysterectomy after previous cone biopsy, and one followed punch biopsy alone (Table 4). In 11 of these 12 cases that were initially diagnosed as CIS by cone biopsy, excision of the lesion was complete in five and incomplete in six. Hysterectomy was performed in two of these cases with incomplete excision, CIS being present in the cervix of one and at the vaginal cuff margin in the other. Clinical and cytology follow-up was excellent in seven of the 12 patients and incomplete in five (Figure 1, cases 1, 6, 8, 10, and 12).

Two of the women who developed invasion (cases 2 and 6), did so without any preceding abnormal cytology, and four of the remaining women (cases 3, 4, 9, and 11) did so within only five months of the reappearance of abnormal cytology. The clinical stage at diagnosis (FIGO 1976) of the 12 patients who developed invasive carcinoma is shown in Table 5. To date, four of these group 1 patients have died from invasive carcinoma of the cervix.

In the authors' view, the subsequent development of invasive carcinoma in the cervix or vaginal vault in the 12 group 1 patients probably represents the development of new carcinoma because they had lengthy periods of normal follow-up cytology after initial management.

The 131 patients in group 2 continued to produce abnormal cytology consistent with cervical neoplasia irrespective of the initial management or the histologic completeness of excision of the lesion. The principal management in this group was by cone biopsy in 88,

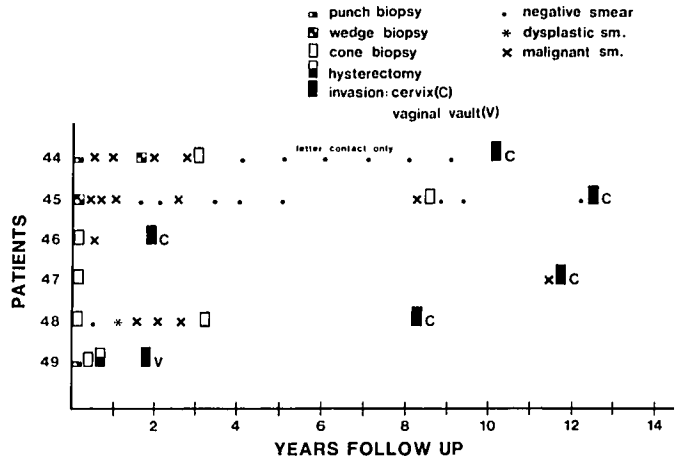

Figure 3. Follow-up details to invasion of six women among 131 group 2 patients with incomplete follow-up who developed invasive carcinoma; five cervix and one vaginal vault after hysterectomy.

total hysterectomy in 33, outpatient punch biopsy alone in five, wedge biopsy preceded by outpatient punch biopsy in three, and wedge biopsy alone in two (Table 4). Excision margins were histologically incomplete in 65 (74%) of the 88 cone biopsies and in all ten outpatient punch and wedge biopsies. Carcinoma in situ was present at the vaginal cuff excision margins in two of the total hysterectomy specimens.

A final diagnosis in this group was established by further biopsy in all patients, except four, at least one year (range one to 19, median six years) after the initial biopsy diagnosis of CIS, by cone biopsy in 78, hysterectomy in 29, or other biopsy in 20 patients (Table 6).

Twenty-nine women developed invasive carcinoma; in 90 CIS persisted, in five dysplasia was evident, and in three no abnormality was found on the final biopsy. Four patients became clinically and cytologically normal after periods of continuing abnormal cytology up to five years after the initial histologic diagnosis, and were not biopsied again. In the 29 women who developed invasive carcinoma (cervix, 20 and vaginal vault, nine), 14 followed initial treatment by cone biopsy, six total hysterectomy, and nine followed management by punch or wedge biopsy (Table 4). Twenty-three of the patients (Figure 2) who developed invasive carcinoma had excellent clinical and cytologic follow-up. In the remaining six patients (Figure 3), follow-up was incomplete.

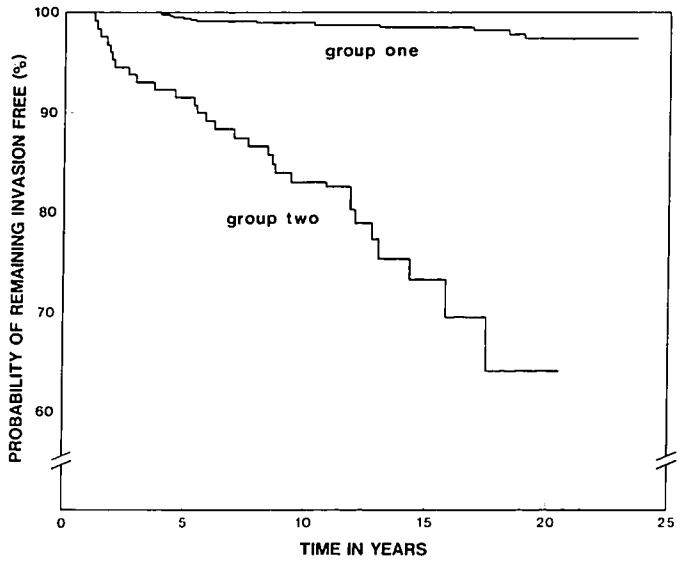

Figure 4. Probability of remaining invasion-free for group 1 and 2 patients at increasing intervals from diagnosis of CIS.

Table 3. Summary of Descriptive Data of the Two Groups

	Group 1	Group 2
Number of patients	817	131
Observed invasion	12	29
'Expected' invasion*	3.81	0.47
Proportion noncaucasian	10%	15%
Median parity	3	3
Median age at diagnosis	36	40

* Expected invasion—calculated by subject-years method from 1975 New Zealand Cancer Registration Statistics.

The presence of continuing abnormal cytology after the initial diagnosis of CIS in the 29 group 2 women who later developed invasive carcinoma, strongly suggests the progression of CIS to invasion rather than the development of a new carcinoma as in group 1 patients.

The clinical stage (FIGO 1976) at diagnosis of the 29 group 2 patients who developed invasive carcinoma is shown in Table 5. At review date, eight of these group 2 patients had died from invasive carcinoma, four of cervix, and four of vaginal vault.

Multiple lower genital tract malignant disease (multifocal disease) is noted in 17 (1.8%) patients, and involved the cervix and vagina in 11 (two group 1 and nine group 2), and the cervix and vulva in six (all six group 1).

Twelve of the 817 (1.5%) group 1 patients and 29 of the 131 (22.1%) group 2 patients developed invasive carcinoma. These figures give a crude relative risk of 15.1. The groups had differing periods of exposure to risk. There was a total of 135,461 woman-months of risk in group 1, and 17,424 woman-months of risk in group 2. These figures indicate incidence rates of 0.89 and 16.64 per 10,000 woman-months, respectively, which gives a relative risk of 18.78. Combining age-specific odds ratios by the Mantel-Haenszel method yielded a relative risk of 18.54 with a 95% confidence interval of 9.68 to 35.48. (The Mantel-Haenszel statistic was 77.65, $P < .0001$.) This figure agrees with the figure of 18.78 found above.

The above methods take no account of the effects of

Table 4. Detailed Patient Management

Management	Group 1		Group 2	
	No. of patients	Development invasion	No. of patients	Development invasion
Cone biopsy and amputation cervix				
Punch and/or wedge, later cone biopsy	131	2	53	4
Cone biopsy	448	7	35	10
Amputation cervix	6			
Total hysterectomy				
Punch and/or wedge biopsy, later TH	34		4	
Cone, later TH	156	2	29	6
Primary TH	27			
Other				
Outpatient punch biopsy only	6	1	5	5
Punch, later wedge biopsy	4		3	2
Wedge biopsy only	5		2	2
Total	817	12	131	29

TH = total hysterectomy.

possible confounding covariates such as race, parity, and age at diagnosis of CIS on the level of risk, nor do they make full use of the lengths of the intervals from diagnosis to invasion or last follow-up. A Cox regression analysis was used to assess the relative contribution of the covariates to changes in level of risk of incidence of invasive carcinoma. Age at diagnosis of CIS was found to be significantly correlated with risk ($P < .0001$), whereas race and parity were not ($P > .1$). The contribution attributable to group membership was also significant ($P < .0001$), and the relative risk for group 1 compared with group 2, allowing for differing ages at diagnosis in the groups, was 24.8 with a 95% confidence interval of 11.76 to 52.14, while a ten-year increase in age at diagnosis in either group had an associated relative risk of 2.5 (1.934, 3.344).

The percentage probability of the occurrence of invasive carcinoma with increasing time is shown for each group in Figure 4, which displays the probability of remaining invasion-free for group 1 and 2 patients at increasing intervals from initial management (Kaplan-Meier estimates).[5]

Discussion

To study the natural history of intraepithelial neoplasia a representative biopsy specimen is required for initial diagnostic purposes, whereas at the same time leaving the remainder of the lesion undisturbed for long-term follow-up. Small biopsies and possibly physiologic trauma can result in eradication of CIS of the cervix.[7] Inadequate or misdirected initial biopsies may, on the other hand, miss areas of significant abnormality such as invasive carcinoma. Accepting these limitations, any examination of the natural history of CIS of the cervix must depend on a representative, though incomplete, biopsy specimen on which to base the inital diagnosis. Thereafter, meticulous long-term follow-up of all patients using techniques such as clinical examination, cytology, and colposcopy, and if indicated, biopsy is required. A final diagnosis can then be established after a further representative biopsy.

The almost universal acceptance of the malignant potential of this lesion has made prospective investigation into the natural progression of CIS ethically impossible. Earlier studies can be criticized on the grounds of the initial histologic diagnosis and the inadequacy and length of follow-up. The present investigation is of women with CIS of the cervix observed in a single institution where, on the basis of follow-up cytology alone, two separate patient groups are available for study—a first and much larger group (817 patients) with normal follow-up cytology and a second smaller group (131 patients) with continuing abnormal cytology at follow-up.

Table 5. Clinical Staging at Invasion

	Stage					Vaginal vault	Total
	Ib (occ)	Ib	IIa	IIb	IIIb		
Group 1	2	4		2	2	2	12
Group 2	14	2	2	1	1	9	29

Table 6. Outcome in Group 2 Patients

Invasive carcinoma cervix and vault	29
CIS	90
Dysplasia	5
No abnormality in biopsy specimen	3
Resolved—no biopsy	4
Total	131

CIS = carcinoma in situ.

A feature of this study is that none of the 617 patients observed in the first 17 years, and only 29 of the 331 in the last five years, have been lost to follow-up.

In the present study, 41 of the 948 (4.3%) women with CIS of the cervix developed invasive carcinoma of the cervix when followed from five to 28 years. On examination of this material, it becomes apparent that patients cluster into two groups. Detailed enquiry showed some overlap between the two groups, but for practical purposes there are clear differences.

Only 12 (1.5%) of the 817 women with normal cytology follow-up after initial diagnosis and treatment subsequently developed invasive carcinoma. This is comparable with the 1.1% incidence of invasion that developed between three and nine years in the 986 cases treated during the years 1960 to 1970 and reported by Kolstad and Klem.[8] Recurrence of CIS in only six (0.7%) of the 817 group 1 patients was significantly less than the 2.1% reported by Kolstad and Klem and is probably related to the authors' classification of patients into two separate groups.

Burchardt and Holzer[9] state that adequately treated CIS is a totally curable lesion. They report no recurrences in 634 cases treated by conization with complete removal of the lesion. However, the reoccurrence of CIS and the development of invasive carcinoma in adequately treated cases is reported by other authors.[8,10] This latter conclusion is strongly supported by evidence in the present study in which five of the 12 patients who had normal cytology after initial management (group 1) later developed invasive carcinoma despite complete removal of the original lesion. However, contrary to what would be expected, of the 139 group 1 patients with incomplete excision of the original lesion, only five (3.5%) later developed invasive carcinoma. Thus, whether or not the lesion is completely excised does not appear to influence the possibility of invasion occurring subsequently.

Because the group 1 patients had normal cytology after initial management, they might be expected to display a similar incidence of invasive carcinoma to that found in the general population. In the present study, the crude incidence of invasive carcinoma was 12 in 817, or 1469 per 100,000. In New Zealand in 1975, the age-standardized incidence for women aged 20 to 75 years, as measured by new invasive carcinoma of the cervix registrations each year, was 18.5 per 100,000. Standardizing the data from the present study to this population yields a figure of 58.2 per 100,000 per year for group 1, and 1141 per 100,000 per year for group 2. These rates have been adjusted for the changing age structure of the population with time using the subject-years method.[11] Thus, patients with normal follow-up cytology after treatment of CIS of the cervix are 3.2 times more likely to develop invasive cervical or vaginal vault carcinoma compared with those women who have never had CIS of the cervix. It is important to note in this study that regular clinical and cytology follow-up of the apparently successfully treated CIS patients did not prevent invasive carcinoma development. In the majority of these women, the carcinoma arose either de novo or within a few months of the first new cytology abnormality, indicating that invasion had not progressed through the expected lengthy premalignant phase. In these cases, it appears that the original lesion was cured by the initial treatment, but that new invasive carcinoma developed in a common field without the expected lengthy premalignant phase.

In the second group of patients with continuing abnormal cytology follow-up after initial diagnosis (and hence, evidence of continuing neoplasia), invasive carcinoma developed in 29 of 131 (22%) patients followed from five to 19 years. These women with continuing abnormal cytology are 24.8 times more likely to develop invasive carcinoma than women of the same age who have normal cytology after diagnosis. In the study of Petersen,[12] 34 of 127 (26.8%) untreated patients developed invasive carcinoma when followed from five months to nine years. Koss and colleagues[7] followed 67 patients for three years and found that four patients (5.9%) progressed to invasion.

However, the reported results of Petersen[12] and Koss et al[7] have not been adjusted for the differing periods of exposure in the populations studied, and thus are difficult to interpret.

Only some patients with CIS of the cervix will develop invasive carcinoma in their lifetime.[7,8,10,12] At the completion of the present study, CIS had disappeared in only 5% (seven of 131) of group 2 women. Regression of CIS should therefore be regarded as a very uncommon event, a point earlier made by Koss et al.[7] This contrasts markedly with the study of Petersen,[12] in which stationary epithelial abnormalities had disappeared in all patients in the course of 15 years. On the other hand, the authors' results clearly indicate that CIS persisted for varying periods up to 19 years in 90 of the 131 group 2 women, with invasion developing in 29 of them.

Only 25 women were managed by a small incomplete diagnostic biopsy and observation alone, but they deserve special comment. Although the biopsy was intended not to eliminate the lesion, it is noted (Table 4) that 15 of the 25 cases (60%) had normal cytology after the biopsy (group 1), and in only one of these 15 cases did invasion occur—some four years later. (Thus, any claim for successful treatment after

limited diagnostic biopsy, eg, colposcope-directed punch biopsy, must be considered in this light). On the other hand, eight of the ten (80%) women with continuing abnormal cytology after limited biopsy (group 2) developed invasive carcinoma over the next one to eight years (median four years).

The importance of continuing to observe patients for a long period has been stressed repeatedly,[7,8,10] and is apparent when the findings of the present study are compared with an earlier report from this hospital in which it was stated that only one patient in 576 (0.2%) developed invasive disease.[13]

The marked differences in the histologic completeness of excision between the group 1 and 2 patients is partly explained by the conservative management of group 2 patients in whom complete excision was not considered a necessity.

Any prospective investigation into the invasive potential of CIS must establish, with as much certainty as possible, that invasive disease is not present at the outset, without, however, removing all potentially affected tissue for histologic examination and thereby destroying the tissue required for later study.[14] In addition to ensuring that invasion was not present at the outset by thorough clinical, colposcopic, and histologic examination of the cervix and upper vagina, the authors have also excluded eight patients found to have invasion within the first year after an initial biopsy that had shown only CIS. In a recent study, 53 of 66 (80%) women who developed invasive disease after ablative treatment for cervical intraepithelial neoplasia did so within one year.[15]

From the data included in the present study, it is possible, from the nature of her cytology follow-up, to estimate the relative likelihood of a woman with CIS to develop invasive carcinoma. In the group 1 patients, 12 of 817 (1.5%) developed invasion, whereas in group 2 patients, 29 of 131 (22%) developed invasion. Statistical examination of the authors' material, using the Cox regression model, indicates there is a markedly increased chance (24.8-fold) of a woman developing invasion if she continues to produce abnormal cytology. These differences were found to be strongly significant ($P < .0001$).

Of the authors' patients with CIS of the cervix, 17 (1.8%) had at some time evidence of malignant disease elsewhere in the lower genital tract. This emphasizes that premalignant or malignant changes in any part of the lower genital tract can be associated with neoplastic change at any time in another part of this field.

At review date, 12 women who presented with CIS of the cervix had died from invasive carcinoma, four of 817 (0.5%) in group 1 and eight of 131 (6%) in group 2. It is, therefore, impossible to escape the conclusion that patients with continuing abnormal cytology after initial management of CIS of the cervix run an unacceptably high risk of developing invasive carcinoma compared with women with continuing normal cytology. It is apparent from Figure 4 that women with cytologic evidence of continuing neoplasia after an initial diagnosis of CIS of the cervix have an 18% chance of developing invasive carcinoma of the cervix or vaginal vault at ten years, and a 36% chance at 20 years.

The present study clearly demonstrates that CIS of the cervix had a significant invasive potential.

References

1. Green GH: Invasive potential of cervical carcinoma in situ. Int J Gynaecol Obstet 7:157, 1969
2. Reagan JW, Hicks DJ: A study of in situ and squamous cell cancer of the uterine cervix. Cancer 6:1200, 1953
3. Richart RM: Cervical intraepithelial neoplasia, Pathology Annual. Edited by SC Sommers. New York, Appleton-Century-Crofts, 1973, pp 301–328
4. Cox DR: Regression models and life tables. J R Statist Soc B 34:187, 1972
5. Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Statist Assoc 53:457, 1958
6. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. JNCI 22:719, 1959
7. Koss LG, Stewart FW, Foote FW, et al: Some histological aspects of behaviour of epidermoid carcinoma in situ and related lesions of the uterine cervix. Cancer 16:1160, 1963
8. Kolstad P, Klem V: Long term follow-up of 1121 cases of carcinoma in situ. Obstet Gynecol 48:125, 1976
9. Burchardt E, Holzer E: Treatment of carcinoma in situ. Evaluation of 1609 cases. Obstet Gynecol 55:539, 1980
10. Creasman WT, Rutledge F: Carcinoma in situ of the cervix. An analysis of 861 patients. Obstet Gynecol 39:373, 1972
11. Berry G: Analysis of mortality by the subject-years method. Biometrics 39:173, 1983
12. Petersen O: Precancerous changes of the cervical epithelium. Acta Radiol 127[Suppl]:74, 1955
13. Green GH: Cervical carcinoma in situ. Aust N Z J Obstet Gynaecol 10:41, 1970
14. Hertig AT: Early concepts of dysplasia and carcinoma in situ. (A backward glance at a forward process). Obstet Gynecol Surv 34:795, 1979
15. Townsend DE, Richart RM, Marks E, et al: Invasive cancer following outpatient evaluation and therapy for cervical disease. Obstet Gynecol 57:145, 1981

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