APPENDIX 7

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.

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 intial 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.

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.

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 biopsy specimen.

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

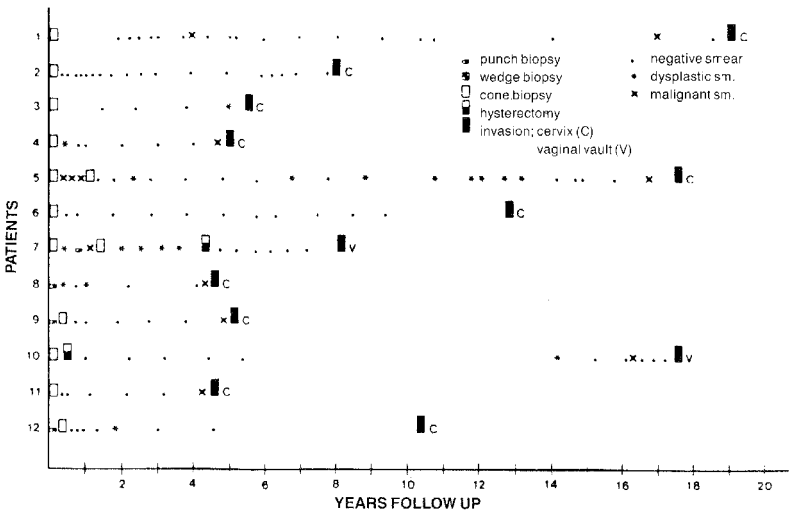

Figure 1. Follow-up details to invasion of 12 women among 817 group 1 patients who developed invasive carcinoma; ten cervix two vaginal vault after earlier hysterectomy.

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.

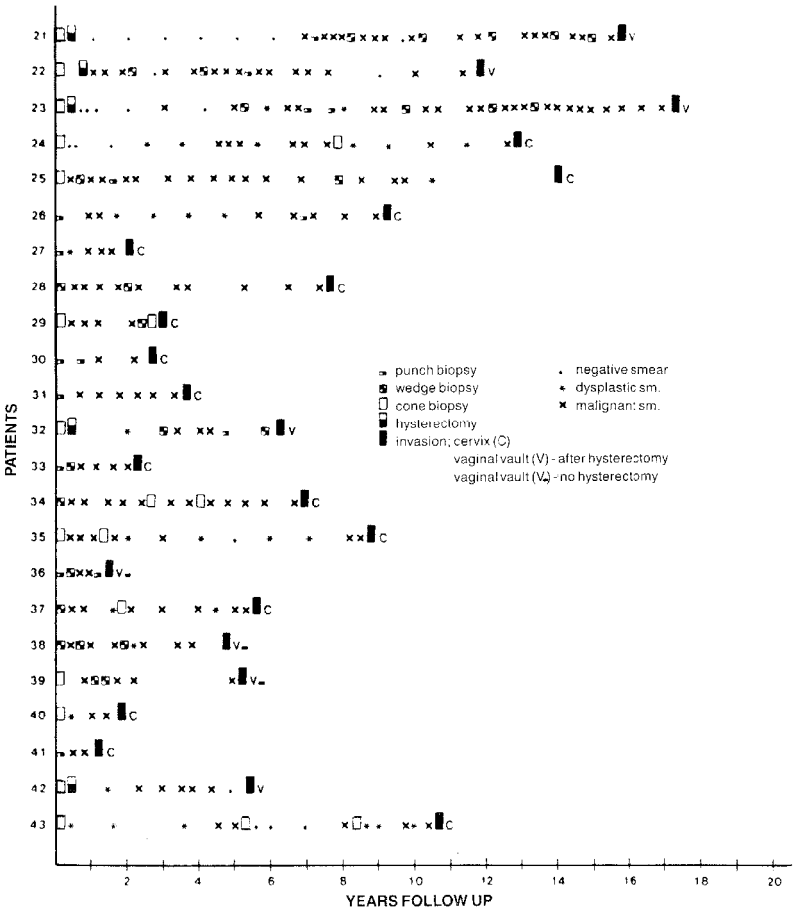

Figure 2. Follow-up details to invasion of 23 women among 131 group 2 patients with good follow-up, who developed invasive carcinoma; 15 cervix and eight vaginal vault.

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.

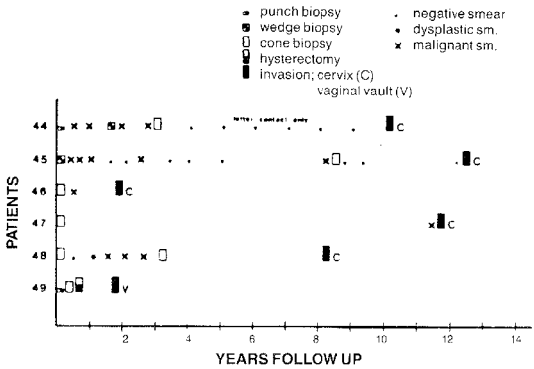

Figure 3. Follow-up details to invasion of six women among 131 group 2 patients with incomplete follow-up who developed invasive carcinoma; five cervix and one vaginal vault after hysterectomy.

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 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, 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.

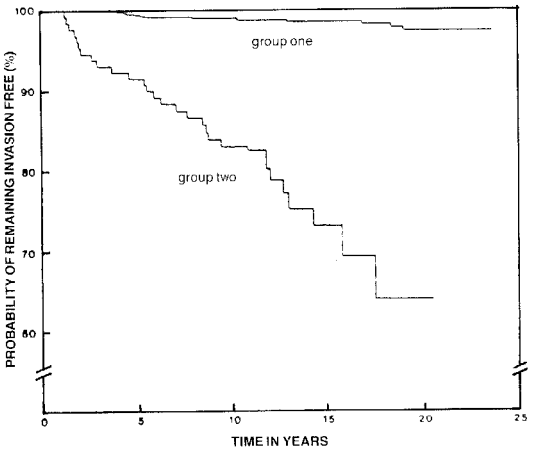

Figure 4. Probability of remaining invasion-free for group 1 and 2 patients at increasing intervals from diagnosis of CIS.

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.

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).

Table 4
Detailed Patient Management

	Group 1		Group 2	
Management	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	6	1	5	5
Wedge biopsy only	5		2	2
Total	817	12	131	29

TH = total hysterectomy.

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 figures agrees with the figure of 18.78 found above.

The above methods take no account of the effects of possible confounding covariates such as race, parity, and 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]

Table 5
Clinical Staging at Invasion

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

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 initial 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 6
Outcome in Group 2 Patients

Invasive carcinoma cervix and vault	29
CIS	90
Dysplasia	90
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.

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APPENDIX 8

CARCINOMA IN SITU OF THE VULVA: A REVIEW OF 31 TREATED AND FIVE UNTREATED CASES

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Thirty six patients with carcinoma in situ of the vulva have been followed from two to 23 years. Among 31 patients managed by surgical excision, there were four recurrences of vulvar carcinoma in situ and one patient developed a vulvar carcinoma 17 years later. Four middle-aged and elderly women managed only by biopsy all progressed to invasive vulvar carcinoma in two to eight years; one additional patient progressed to invasion after inadequate primary treatment. These last five cases all represented multifocal lower genital tract neoplasia. Untreated vulvar carcinoma in situ, when seen as part of a multifocal lower genital tract neoplastic process, in middle and later life is likely to progress to invasion. (Obstet Gynecol 68:499, 1986)

Carcinoma in situ of the vulva was once regarded as an uncommon condition, but recent reports indicate that the prevalence is increasing.[1,2] Previously considered a disease of middle and late life, the recent rise in frequency has been made up largely of younger women [2,3] and this trend coincides with an increase in certain genital infections, especially those with human papilloma virus and herpes simplex virus type 2.[4]

There is conflicting evidence regarding the invasive potential of vulvar carcinoma in situ[5,6] although most reports indicate that progression to invasion is a very uncommon event.[7] Lavery [8] has stated recently that the natural history of vulvar carcinoma in situ is unknown, presumably because so few reported cases have been managed by limited biopsy and observation alone.

In this study the long-term follow-up of 36 women with carcinoma in situ of the vulva is presented, including four patients managed by biopsy and observation alone and a fifth patient in whom the lesion was incompletely excised after a lengthy period of observation. This conservative approach was an extension of a study of the conservative management of carcinoma in situ of the cervix.[9] Of the remaining cases, 30 were treated by surgical excision and one by local irradiation.

Materials and Methods

The clinical records of the 36 women diagnosed histologically as having carcinoma in situ of the vulva between 1962 and 1983 were reviewed and followed at the National Women's Hospital, Auckland, New Zealand.

Diagnosis was based on the criteria of the International Society for the Study of Vulva Disease.[10] Evidence of full thickness change to a neoplastic cell population that shows anaplasia, pleomorphism, abnormal mitoses, dyskeratosis, pilosebaceous involvement, and degrees of surface maturation including hyperkeratosis and parakeratosis prompted diagnosis. Less commonly, full thickness change may not be present but rete ridges show epithelial pearls at their tips. Cases of Bowenoid papulosis and Bowenoid dysplasia were excluded because these lesions are considered to have clinical, histologic and biologic differences from those of carcinoma in situ.[11,12] Cases of Paget disease of the vulva also were excluded. The initial diagnosis was made on excised specimens or multiple biopsies.

Koilocytotic atypia was observed in most cases at or near the surface in the lesion or at its edges and was regarded as histologic evidence of human papilloma virus infection.

This atypia was defined according to the criteria of Casas-Cordero et al[13] and Reid et al,[14] namely large cells with contracted irregular hyperchromatic nuclei surrounded by clear and transparent cytoplasm together with multinucleated cells and dyskeratosis.

Histologic specimens after formalin fixation were processed in the usual manner and at least three step serial sections were cut from each block and stained with hematoxylin and eosin. The reviewed material ranged from two blocks in a single vulvar biopsy to up to 40 in some cases of multifocal lower genital tract neoplasms. Sections were recut where necessary.

Table 1
Management and Outcome of 36 Women With Vulvar Carcinoma In Situ

Initial management	*N*	Outcome	*N*
Local excision	26	Recurrence CIS	4
Simple vulvectomy	4	Vulvar carcinoma*	1
Irradiation	1		
Biopsy and observation only	4	Progression to	
Delayed primary excision	1	vulvar carcinoma	5
Total	36		

CIS = carcinoma in situ.
* New carcinoma arising in susceptible field and not progression.

All cases were followed to death or the conclusion of the study in June 1985 with the exception of one patient who was lost to follow-up. Follow-up duration ranged from two to 23 years.

Management was determined by the clinician responsible for the case. Initial treatment in 26 was by local excision, in four simple vulvectomy, and in one local irradiation. Five cases were treated conservatively, four being managed by biopsy and observation alone, while a fifth case was managed by biopsy and observation for four years before having a simple vulvectomy with incomplete excision of the carcinoma in situ (Table 1).

Results

The ages of patients at the time of initial diagnosis ranged from 24 to 88 years (median 52). Before 1976, all of the women presenting with vulvar carcinoma in situ were over 40 years of age but since then, nine of the 20 (45%) additional patients have been younger than this. Twenty four cases were diagnosed in the years 1962 to 1980 and 12 cases in the three-year period 1981 to 1983. There were 32 Europeans and three Maoris. Four patients had previously been treated for genital tract condylomas and two patients had had genital herpes simplex. Eight cases (22%) were asymptomatic, the lesion being detected as part of a routine gynecologic examination or follow-up of other lower genital tract malignancy. In three cases the lesion was principally in the perianal region. One patient had drug-induced immunosuppression for treatment of an autoimmune disorder.

Nineteen of the 36 (52%) cases had at some time an associated lower genital tract malignancy. Vulvar carcinoma in situ was associated with carcinoma in situ of the cervix in 12 cases, carcinoma of the cervix in four cases, carcinoma in situ of the cervix and the vagina in one case, carcinoma of the vagina and carcinoma in situ of the cervix in one case, and with carcinoma of the vagina in one case. None of these lesions were contiguous with the exception of one patient in whom carcinoma in situ extended from the cervix along the entire vagina to the vulva. In all cases, the development of in situ or invasive disease elsewhere in the genital tract preceded or was synchronous with the diagnosis of the

vulvar carcinoma in situ. The site and type of associated lower genital tract neoplasia and the time of development of this associated neoplastic process in relation to the development of the vulvar carcinoma in situ is shown in Figure 1.

Extragenital tract malignancy (pancreas one, kidney one) developed in two cases some years after the diagnosis of vulvar carcinoma in situ. Excision margins were clear in all cases treated by simple vulvectomy and 24 of the 26 cases treated by local excision.

Koilocytotic atypia was observed in 25 of the 36 (70%) initial vulvar specimens, including 18 of the 19 (95%) cases with multiple lower genital tract neoplasia. It also was present when further biopsy specimens were taken in these cases. Koilocytotic atypia has been found with increasing frequency in recent years, being noted in 14 of 23 (60%) cases in the first 20 years and 11 of 12 (92%) cases in the last two years of the study.

Early in the study one elderly woman with contiguous carcinoma in situ extending from the cervix to the vulva was treated with local irradiation but died of intercurrent disease a year later. Topical 5-fluorouracil (5-FU) cream was used to patient tolerance in three cases but in none was there any improvement and surgical excision became necessary. Of the 26 cases managed initially by local excision of the macroscopically affected skin, there were four recurrences of vulvar carcinoma in situ. In two of these, excision margins had been involved. One of these cases subsequently underwent simple vulvectomy but in spite of this has developed two further recurrences requiring local excision. In none of the cases treated initially by local excision did invasive vulvar carcinoma subsequently occur.

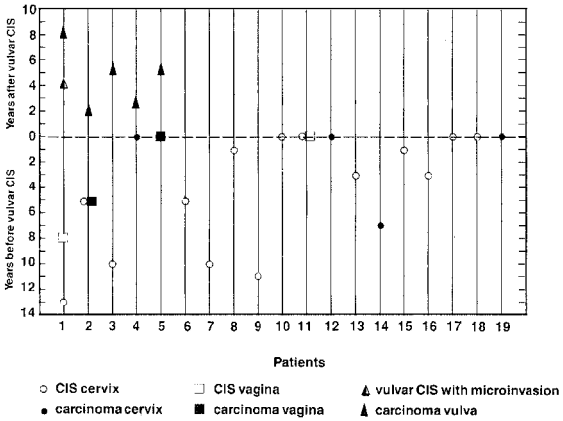

Figure 1. The site, type, and time of development of the 19 cases of associated lower genital tract neoplasia in relation to the development of vulvar carcinoma in situ (CIS).

Four women were initially treated with simple vulvectomy. One of these patients had a further vulvar biopsy 12 years later, which showed an epithelial dystrophy without atypia. Five years after this she developed an early invasive vulvar carcinoma. Thus, invasive vulvar disease occurred in only one of the 31 treated cases (3%).

Spontaneous regression was not observed in any patients in this study.

Four patients were managed by biopsy and observation alone, and all four progressed to invasive vulvar carcinoma over the next two to eight years. One additional patient was managed by biopsy and observation for four years before undergoing simple vulvectomy with incomplete excision of the carcinoma in situ; 11 months later, invasive carcinoma

developed at the external urethral meatus. These five cases, which progressed to invasive carcinoma all represented multifocal lower genital tract malignancy and all exhibited histologic evidence of koilocytotic atypia.

Case 1

This 43-year-old woman had a total abdominal hysterectomy for carcinoma in situ of the cervix in 1960. The lesion was completely excised. Normal vaginal vault cytology was recorded for five years, at which time she developed abnormal vaginal vault cytology and biopsy evidence of dysplasia. This was not treated and she continued to have positive vaginal vault cytology until 1970, when a further vault biopsy showed evidence of carcinoma in situ. The next year, a quite separate area of abnormal skin was noted on the posterior vulva and a representative biopsy confirmed vulvar carcinoma in situ. The separate vulvar and vaginal abnormalities persisted until 1977 when she was treated with a vulvovaginectomy. Histology showed vulvar carcinoma in situ with several foci of microinvasion. She continued to have positive cytology from unexcised abnormal skin at the external urethral meatus and biopsy in 1981 confirmed a carcinoma from which she subsequently died.

Case 2

This 45-year-old woman presented in 1967 with an invasive carcinoma in the vaginal fornix and associated carcinoma in situ of the cervix. Treatment was by local irradiation. She continued to have negative clinical and cytology follow-up until 1972 when a representative biopsy of a granular area on the labium minora showed carcinoma in situ. The vulvar lesion persisted and a further biopsy a year later again confirmed carcinoma in situ. At the same time, vaginal vault curettings showed evidence of vaginal vault carcinoma in situ. The vulvar lesion persisted, and a biopsy in 1974 showed invasive vulvar carcinoma from which the patient died in 1976.

Case 3

This 63-year-old patient was treated with irradiation and Wertheim hysterectomy in 1960 for stage 1a carcinoma of the cervix. She had negative clinical and cytologic follow-up until 1963 when a vaginal vault biopsy taken as a result of positive cytology showed a "dysplastic" epithelium. The abnormal vaginal vault cytology persisted. She complained of vulvar pruritus from 1965 and vulvar biopsy specimens in 1970 and 1972 showed carcinoma in situ. Invasive vulvar carcinoma was demonstrated histologically in 1975 and a radical vulvectomy performed. In 1977 she developed invasive carcinoma at the external urethral meatus from which she died.

Case 4

This 58-year-old patient presented in 1972 with a stage 3b carcinoma of the cervix and carcinoma in situ of the vulva. She received local irradiation for the cervical carcinoma but no treatment for the vulvar carcinoma in situ. In 1975 she developed an invasive carcinoma of the vulva, which was treated by vulvectomy. She died of an intercurrent illness in 1983, there being no evidence of recurrent neoplastic disease.

Case 5

This 64-year-old woman presented in 1974 with a ten-year history of intermittent postmenopausal bleeding. Extensive vaginal carcinoma was found and treated with local irradiation. At the same time a noncontiguous vulvar lesion was biopsied, which showed vulvar carcinoma in situ. The vulvar lesion was not treated and persisted during follow-up. A further biopsy in 1979 showed carcinoma in situ with microinvasion, and a simple

vulvectomy was performed. Microinvasive tumour foci were present at the excision margin. Less than a year later, an invasive carcinoma was noted at the external urethral meatus. She died after anterior exenteration.

Discussion

This series has shown a strong correlation between vulvar carcinoma in situ and other lower genital tract malignancy, a striking association with human papilloma virus infection, and a recent increase in the frequency of the condition in younger women. In addition, it provides evidence that the untreated lesion in women of middle and later life has a significant invasive potential.

The observed association of vulvar carcinoma in situ with other lower genital tract malignancies is very much higher (52%) than the approximate 25% in most previous reports.[2, 15] This may partly reflect a thorough follow-up system, which is possible in an insular oncology unit. However, a similarly close association has been noted in young women by Benedet.[3]

Twenty-three percent of the patients studied herein were asymptomatic, a proportion similar to that reported by others.[1-3]

Thirty years ago, Lewis [6] stated that all true cases of Bowen disease left untreated progressed eventually to invasion, although it is difficult to establish the basis for his claim. Recent studies report the rate of progression to be between 2 and 4%.[2, 15] However, these contrasting statements have quite different bases. Whereas Lewis implied a strict "no treatment" approach, allowing the natural history to be expressed, more recent authors comment on the final outcome after treatment. To study the natural history of intraepithelial neoplasia, a representative biopsy is required for initial diagnostic purposes, while at the same time leaving the remainder of the lesion undisturbed for long-term follow-up. The authors are unaware of previous reports of patients without other modifying factors such as immunosuppression managed in this way. Friedrich[15] described a severely immunosuppressed 21-year-old woman who progressed without treatment to invasion in one year, and Ostor [16] described an 81-year-old woman who progressed to invasion in four years after systemic Bleomycin (itself an immunosuppressant). All other reported instances of progression of vulvar carcinoma in situ to invasion appear to have occurred despite local treatment.[2-23] It is apparent in some cases that the original lesion was incompletely excised,[20] while in others a "new" carcinoma developed either in the previously treated region or in part of the common field derived from the cloaca, which includes the external urethral meatus and perianal skin.

Crum[22] has reported the development of lower genital tract carcinoma in five women previously treated for vulvar carcinoma in situ. However, in three of these cases developing vulvar carcinoma alone, the invasion occurred within one year of the diagnosis of vulvar carcinoma in situ, raising the possibility of "missed invasion" at the original biopsy. Invasion developing within one year of the diagnosis of carcinoma in situ possibly represents a "missed invasion" rather than progression. This view is supported by Caglar[21] who reported the presence of invasion as an incidental finding in three cases where vulvar biopsy had demonstrated only carcinoma in situ. The criticism that there may have been a "missed invasion" at the original biopsy can best be avoided by ensuring that an adequate representative biopsy (ideally with colposcopic assessment) be performed, that the biopsy be step serial sectioned, and that at least one year should elapse between the initial biopsy and the first appearance of invasive disease.

Recurrence of vulvar carcinoma in situ occurred in four of the 31 treated cases. One was similar to that reported by Caglar[21] in which there were multiple recurrences of vulvar carcinoma in situ despite complete excision including simple vulvectomy. Vulvar carcinoma developed in one of the current treated cases (3%) in dystrophic skin 17 years

after a simple vulvectomy for carcinoma in situ. The authors do not believe that this represents "progression" of carcinoma in situ and should be regarded as a new carcinoma arising in a field at risk. The 2 to 4% incidence of progression in treated cases reported by other authors [2, 15] are possibly other examples of the development of a new carcinoma in a field at risk or missed invasion rather than true progression.

In this series, four of the five cases of vulvar carcinoma in situ progressing to invasion had received pelvic irradiation for cervical or vaginal carcinoma in the three to 15 years before the development of vulvar carcinoma. In the fifth case, progression to invasion occurred in the absence of irradiation. Preceding irradiation is also reported in three other cases of progression to invasive carcinoma.[2, 17] The common factor appears to be multifocal lower genital tract neoplasia irradiation having been used in the majority of cases. Evidence for the role of irradiation as a specific factor influencing progression to invasion therefore remains uncertain.

In the present study, those women with evidence of koilocytotic atypia were significantly younger than those women without it. In addition, koilocytotic atypia was noted in all but one of the 19 women (including the five who progressed to invasion) in whom vulvar carcinoma in situ was part of a multifocal lower genital tract neoplasia. There is increasing evidence to suggest a role for human papilloma virus infection in lower genital tract carcinogenesis, but at present it is not possible to prove an etiologic relationship. Crum[22] has identified a group of younger women with carcinoma in situ of the vulva and evidence of human papilloma virus infection who have a low risk of progression to cancer and an older group with a variable history of condyloma and a higher risk of developing anogenital carcinoma. The role of herpes simplex virus is not yet clear. Herpes simplex virus type 2 antigens have been demonstrated by Kaufman[24] in nine of ten women with vulvar carcinoma in situ. The clinical and pathological similarity between intraepithelial neoplasia of the cervix and vulva and the demonstration of herpes simplex virus type 2 antigens and papilloma virus antigen suggests both are oncogenic factors possibly acting in a synergestic fashion. If venereal factors are involved in the pathogenesis of vulvar carcinoma in situ, it is surprising that there has been no reported significant increase in penile carcinoma in situ.

In the authors' view, all women with vulvar carcinoma in situ in middle and later life should be treated with conservative local excision, particularly if there is other evidence of preceding or concurrent lower genital tract neoplasia. Although a small proportion of recurrences will occur, mutilating vulvectomy is avoided. It also provides tissue that allows carcinoma to be excluded. There is only a limited case for the use of 5-FU cream on the vulva. Laser therapy should perhaps be restricted to younger women with multiple vulvar lesions in whom the likelihood of progression to invasion is very small. Lifelong follow-up of the entire genital tract is mandatory.

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