

## Coexistent Squamous Cell Carcinoma and Adenocarcinoma of the Uterine Cervix

YEW CHEONG CHOO, M.D.,<sup>1</sup> AND BERNARD NAYLOR, M.D.

*Division of Gynecologic Oncology, Departments of Obstetrics and Gynecology and Pathology, University of Michigan Hospital, Ann Arbor, Michigan 48109*

Received August 12, 1981

The clinical and pathological features of 20 patients with coexistent squamous cell carcinoma and adenocarcinoma of the uterine cervix have been analyzed. Various combinations of *in situ* and invasive carcinomas were found. Located adjacent to each other and at times intermingling, these lesions probably originated from the subcolumnar reserve cells of the transformation zone. They are early lesions and may be precursors of adenosquamous and mucoepidermoid carcinomas of the cervix. The diagnosis of these double carcinomas depends upon being aware that the two entities may coexist in the same cervix. Treatment is conventional, and the prognosis is not worsened by the presence of the two types of neoplasms.

### INTRODUCTION

The simultaneous occurrence of squamous cell carcinoma (SCC) and adenocarcinoma (ADC) of the uterine cervix has been infrequently reported [1-5]. This combination is the rarest and the most unusual form of cervical carcinoma. Melnick *et al.* [1] first reported such cases in 1957; Dougherty and Cotten [3] grouped them as combined or "mixed" carcinomas, and Abell [6] classified them as a histologically distinct type of cervical carcinoma. The histogenesis of synchronous SCC and ADC of the cervix remains speculative. Some authors have suggested that they are two separate diseases and that their combined presence is coincidental [3], whereas others [4,6] believe that they arise from a common cell line, most likely the multipotential subcylindrical or reserve cells of the transformation zone. This study pertains to a clinical and pathological analysis of such patients diagnosed in one institution over a 27-year period.

### MATERIALS AND METHODS

From January 1950 through December 1976, 502 patients with ADC and 2175 patients with SCC of the cervix, including their *in situ* variants, were treated at the University of Michigan Hospital. Twenty of these patients were identified from the files of the Tumor Registry as having synchronous SCC and ADC. We

<sup>1</sup> Present address and to whom requests for reprints should be addressed: Department of Obstetrics and Gynaecology, Queen Mary Hospital, University of Hong Kong, Hong Kong.

have studied their presenting symptoms and signs, the diagnostic methods that were used, and the treatment that was given; we also made note of any hormonally related etiologic factors. We reviewed the histopathological sections and completed a follow-up of the patients through January 1981. Cases of adenosquamous and mucoepidermoid carcinoma of the cervix were excluded from the study.

The pathological identification was made on the basis of the presence of two morphologically distinct carcinomas in separate locations in the cervix. Furthermore, when there was early intermingling of the two components, a morphological transition from one form to another had to be absent, and the architectural distinctiveness of each component had to be preserved.

## RESULTS

Three categories of coexistent SCC and ADC were recognized: SCC and ADC *in situ*, SCC and ADC where one component was *in situ* and the other was invasive, and SCC and ADC where both components were invasive (Table 1).

Five patients had simultaneous SCC and ADC *in situ* (Fig. 1). Their average age was 35.2 years and their mean parity was 1.4. Symptoms and signs were nonspecific. Three patients had a diagnostic cone biopsy because of an abnormal cervical smear; the fourth case was identified by biopsies of an ulcerated area on the cervix. All of these four patients subsequently underwent hysterectomy. The specimens showed no residual carcinoma in one, and residual SCC and ADC *in situ* in another; the remaining two patients each had residual SCC and ADC *in situ*. The fifth case was diagnosed incidentally following an exenteration procedure for a recurrent vulvar carcinoma. All patients are alive with no apparent disease 5–17 years after treatment. One patient, however, developed SCC *in situ* of the upper vagina which was surgically excised.

Two patients had simultaneous ADC *in situ* and invasive SCC diagnosed by cone biopsy because of abnormal cervical smears. In both, no clinically apparent lesion was recorded. One patient was treated by irradiation; the other underwent radical hysterectomy. In the latter patient, both the cone biopsy and the hysterectomy specimens showed areas of SCC *in situ* and invasive SCC accompanied by foci of ADC *in situ*. The patient died of recurrent carcinoma 3 years later. The other patient developed SCC of the vulva 10 years later and is alive 2 years after radical vulvectomy.

Five patients had synchronous SCC *in situ* and invasive ADC (Fig. 2). Their average age was 53 years and mean parity was 4.6. A history of prior use of oral contraceptives was elicited in one patient. Four patients had abnormal

TABLE 1  
TYPES OF COEXISTENT SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA OF THE CERVIX

Squamous carcinoma and adenocarcinoma <i>in situ</i>	5
Mixed carcinoma <i>in situ</i> and invasive carcinoma	
Adenocarcinoma <i>in situ</i> and invasive SCC	2
Squamous carcinoma <i>in situ</i> and invasive ADC	5
Invasive SCC and invasive ADC	8
Total	20

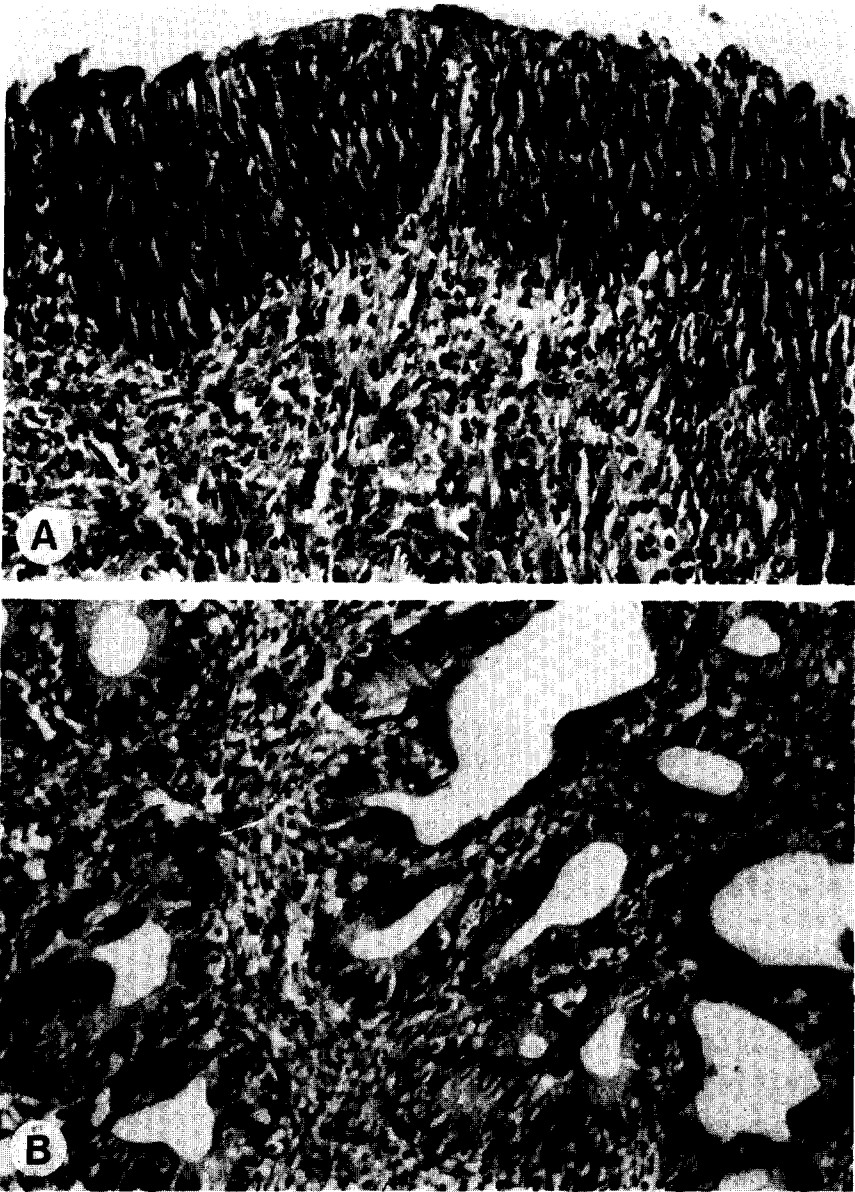


FIG. 1. (A) Squamous cell carcinoma *in situ* (H&E,  $\times 235$ ). (B) Adenocarcinoma *in situ* (H&E,  $\times 200$ ).

cervical smears only. The diagnosis of double neoplasms was made by cone biopsy in three cases and by direct biopsies in the other. The fifth patient had an initial cone biopsy which showed invasive ADC; however, subsequent radical hysterectomy also revealed a distinct focus of SCC *in situ* bordering the invasive ADC. The treatment consisted of radical surgery in three and radiotherapy in two patients. Follow-up data revealed that one patient died 3 years after initial

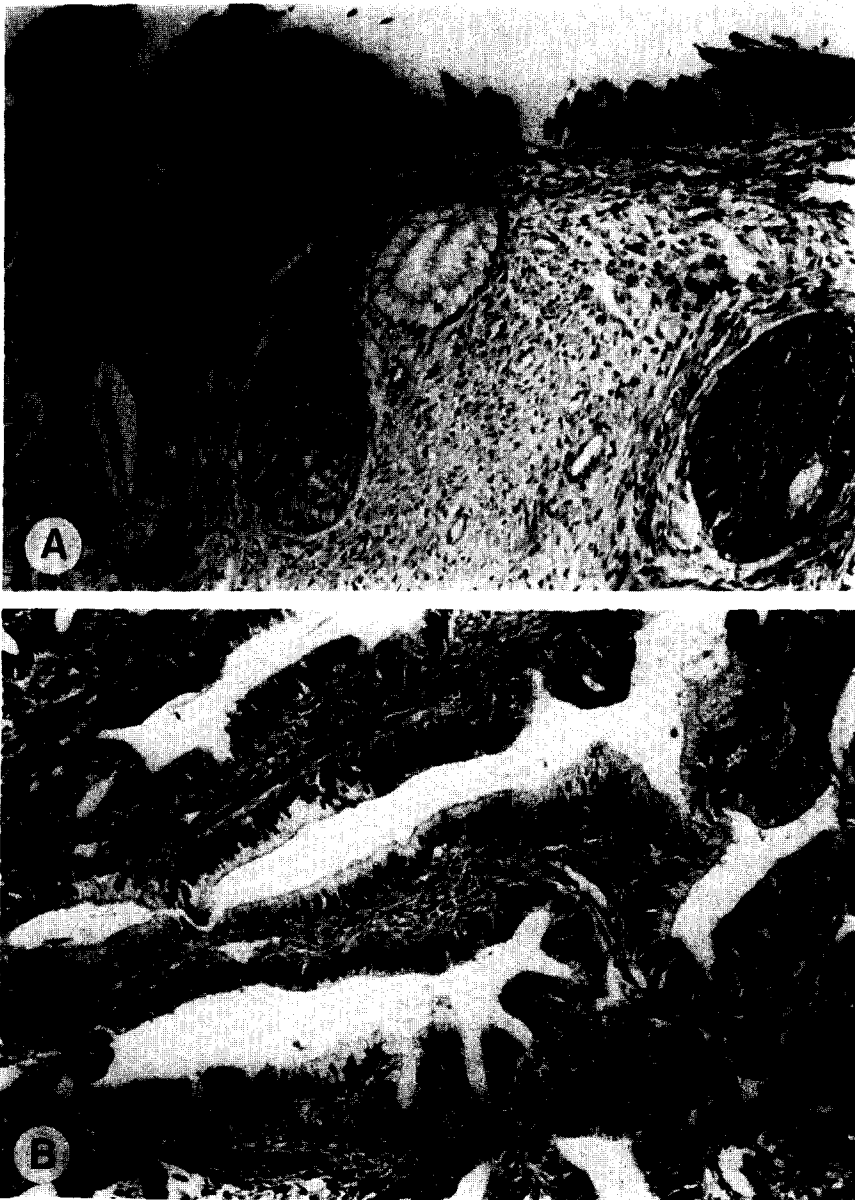


FIG. 2. (A) Squamous cell carcinoma *in situ* with crypt involvement (H&E,  $\times 160$ ). (B) Well-differentiated, invasive endocervical adenocarcinoma (H&E,  $\times 160$ ).

treatment due to recurrent disease and that the remaining four patients are alive for an average of 10.2 years after treatment.

Eight patients had synchronous invasive SCC and invasive ADC (Figs. 3 & 4). Their average age was 57.3 years and their mean parity was 3.5. One case was diagnosed during the first trimester of pregnancy. Some cervixes were described as showing an "erosion," an "ulcer," or a "growth." In most of the cases, however, cancer

was not clinically suspected. Four patients were detected on the basis of an abnormal cervical smear. The lesions were diagnosed by cone biopsy in six patients and by direct biopsies in two patients. In three patients, areas of SCC *in situ* were also identified in addition to the invasive SCC. The carcinomas were confined to the cervix in all except one patient who had evidence of neoplasm extending to the pelvic sidewall. One patient was treated by radical hysterectomy, the rest by irradiation. Follow-up revealed that two died from the carcinoma, one 2 and the other 3-years later; two died from nonrelated diseases, one 10 and the other 13 years later; and the remaining four are alive with an average survival of 9.5 years after treatment.

### DISCUSSION

It is noteworthy that in all of the cases we analyzed, two distinct foci of origin of the carcinomas were demonstrable and that these foci were always adjacent to each other. In a few instances, early mingling at the interphase was noted, yet separate origins of the two types of neoplasm without any transition could still be observed. Such juxtaposition of the two neoplasms and their tendency to collide strongly suggest an origin from a common cell type rather than from different kinds of progenitor cells. The most likely cell of origin is the subcolumnar reserve cell located in the transformation zone. These multipotential cells may differentiate into squamous cells or gland cells.

The absence of any clinical suspicion of cancer in most of the patients with the invasive carcinomas, the concomitant presence of the *in situ* counterpart in some of the invasive carcinomas, and the need to rely on cone biopsy for the diagnosis suggest that these double carcinomas are usually early lesions. It is also possible that such double-primary carcinomas may be the precursor of adenosquamous and mucoepidermoid carcinomas. It is postulated that when such double lesions remain undetected the two types of carcinomas collide and become intimately mixed, which precludes any subsequent identification of two separate components. When this happens, adenosquamous carcinoma is likely to be diagnosed or, if there is predominant development of a squamous component with the glandular component remaining rather unobtrusively as only mucin-secreting cells, a diagnosis of mucoepidermoid carcinoma will be made.

We suggest, therefore, that double-primary SCC and ADC and adenosquamous and mucoepidermoid carcinomas of the cervix are a group of mixed carcinomas that originate from the subcolumnar reserve cells of the transformation zone, and that the double-primary carcinomas are forerunners of adenosquamous and mucoepidermoid carcinomas.

In carcinoma of the cervix of the mixed variety, the hormonal influence of pregnancy or oral contraception has been implicated as causative factors [7]. Such possible predisposing factors were recognized in only 2 of the 20 patients in this study.

Simultaneous SCC and ADC of the cervix probably occur more frequently than has been realized. In a retrospective review of 230 cases of ADC of the cervix, Maier and Norris [5] found coexistent squamous intraepithelial neoplasia in 43% of the patients. Similarly, Shingleton *et al.* [8] found mixtures of invasive

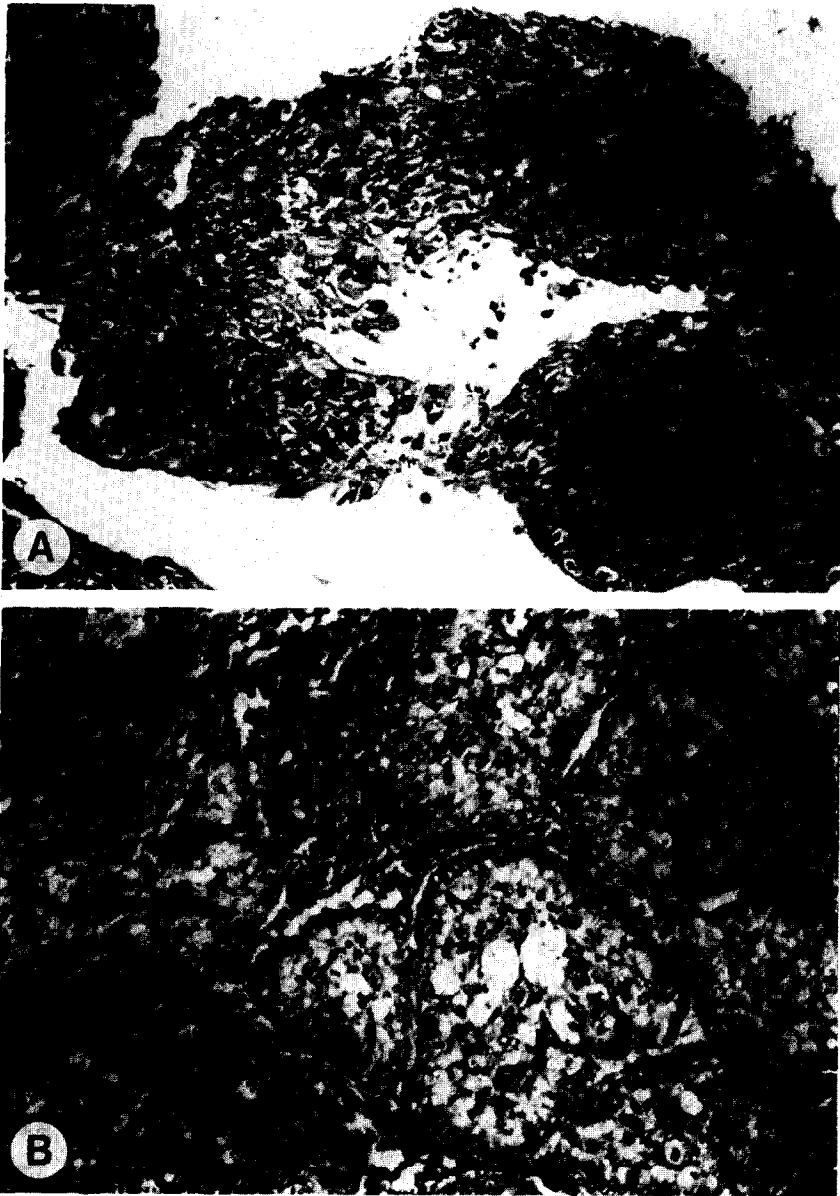


FIG. 3. (A) A fragment of the invasive squamous cell carcinoma (H&E,  $\times 160$ ). (B) Invasive adenocarcinoma (H&E,  $\times 140$ ). (C) Invasive adenocarcinoma next to a focus of invasive squamous cell carcinoma, bottom left (H&E,  $\times 160$ ).

ADC and invasive SCC in one-third and associated squamous intraepithelial neoplasia in one-tenth of 137 patients analyzed with invasive ADC of the cervix. When such double lesions occur, they do not influence the mode of treatment; however, their detection and analysis should shed more light on the histogenesis of cervical carcinoma, particularly of the mixed variety.

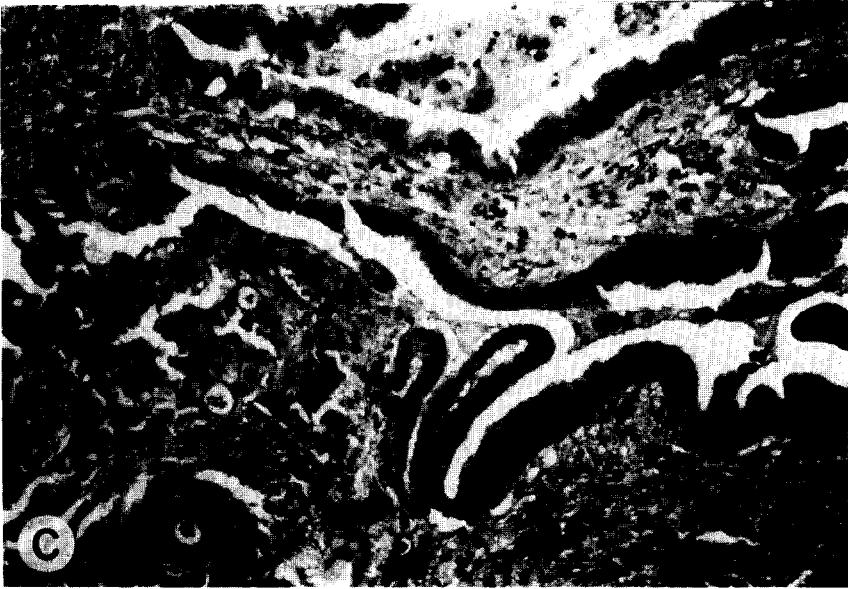


FIG. 3—Continued.

#### REFERENCES

1. Melnick, P. J., Lee, L. E., Jr., and Walsh, H. M. Endocervical and cervical neoplasms adjacent to carcinoma in situ, *Amer. J. Clin. Pathol.* **28**, 354–374 (1957).
2. Abell, M. R., and Gosling, J. R. G. Gland cell carcinoma (adenocarcinoma) of the uterine cervix, *Amer. J. Obstet. Gynecol.* **83**, 729–755 (1962).
3. Dougherty, C. M., and Cotten, N. Mixed squamous-cell and adenocarcinoma of the cervix. Combined, adenosquamous, and mucoepidermoid types, *Cancer* **17**, 1132–1143 (1964).
4. Laughlan, S. C., and Penner, D. W. Simultaneous adenocarcinoma in situ and epidermoid carcinoma in situ. Report of two cases, *Cancer* **12**, 2250–2254 (1967).
5. Maier, R. C., and Norris, H. J. Coexistence of cervical intraepithelial neoplasia with primary adenocarcinoma of the endocervix, *Obstet. Gynecol.* **56**, 361–364 (1980).
6. Abell, M. R. Invasive carcinomas of uterine cervix, in *The uterus* (H. J. Norris, A. T. Hertig, and M. R. Abell, Eds.), Int. Acad. Pathol. Monogr., Williams & Wilkins, Baltimore, pp. 432–456 (1973).
7. Glucksmann, A. Relationship between hormonal changes in pregnancy and development of mixed carcinoma of uterine cervix, *Cancer* **10**, 831–837 (1957).
8. Shingleton, H. M., Gore, H., Bradley, D. H., and Soong, S. J. Adenocarcinoma of the cervix. I. Clinical evaluation and pathological features, *Amer. J. Obstet. Gynecol.* **139**, 799–814 (1981).