# Adenocarcinoma of the Uterine Cervix

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***Background:*** **Adenocarcinoma of the uterine cervix is an increasingly common cervical neoplasm that has received little attention in the primary care literature. The purpose of this paper is to describe an illustrative case that provides an excellent opportunity to review the symptoms, diagnostic pitfalls, treatment options, and prognosis of this important disease.**

***Methods:*** **Case report is described, along with results of a literature review using MEDLINE and pertinent references from retrieved articles.**

***Results:*** **The relative incidence of cervical adenocarcinoma has risen from 5 to 10 percent of all cervical neoplasms in the 1950s to 10 to 20 percent in recent series. Some studies have also reported an increasing absolute incidence linked to widespread oral contraceptive use. The diethylstilbestrol-associated clear-cell variant accounts for only 2 to 3 percent of cases. About 10 percent of patients have only a nonbloody vaginal discharge. Cervical adenocarcinoma might be more easily missed on a Papanicolaou smear than squamous cell dysplasia and cancer, and it has no characteristic colposcopic appearance. The prognosis is excellent with early detection.**

***Conclusions:*** **Family physicians should maintain a high index of suspicion for cervical adenocarcinoma when symptoms suggest this disease regardless of Papanicolaou smear results (J Am Board Fam Pract 1997;10:36-42).**

Adenocarcinoma of the uterine cervix, an uncommon neoplasm in the past, has increased in relative and perhaps absolute incidence in the last 20 years.[1-30] Although this trend is well-documented in gynecologic and oncology journals, it has not been addressed in the family medicine literature. The prognosis for patients with cervical adenocarcinoma is excellent when the disease is detected early, but diagnosis is difficult unless the primary care physician is vigilant when symptoms suggest this disease. The purpose of this review is to alert family physicians to the clinical signs, symptoms, and diagnostic pitfalls of this increasingly important malignancy.

## Methods

After a case report of cervical adenocarcinoma is described, the results of a computerized MEDLINE search from 1966 to 1995 are discussed. The MeSH headings "cervix neoplasms" and "adenocarcinoma" were combined using the "AND" function. The ensuing set of references was limited by the "human" and "English language only" functions. Relevant articles were then selected by reviewing the titles and abstracts. References from reviewed articles were also checked for relevant citations not found on MEDLINE.

## Case Report

A 34-year-old woman complained of a 1-month history of copious, clear vaginal discharge. Her menstrual cycles were regular, and there was no history of intermenstrual bleeding or spotting. She noted no foul odor to the discharge and no dysuria, urinary frequency, or urgency. There were no risk factors for sexually transmitted diseases. She was not using any birth control, but she did report using oral contraceptives continuously between the ages of 19 and 24 years. She did not smoke and had not been exposed to diethylstilbestrol in utero. Specimens for previous Papanicolaou smears were adequate, and the results were normal; the most recent one had been performed 6 months earlier.

When examined vaginally, she had copious clear mucoid discharge at the introitus, which was

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apparent even before speculum insertion. Findings on an external genital examination were unremarkable. Examination using a speculum showed a normal-appearing vaginal canal and a cervix that appeared somewhat diffusely friable. A slightly raised, condyloma-like lesion was noted at about 11 o'clock near the tranformation zone. Findings on bimanual and rectovaginal examinations were unremarkable. Potassium hydroxide and saline wet preparation slides of the discharge showed no abnormalities. Because there was no clear explanation for the discharge after initial examination, the patient was referred for colposcopy. The presumptive diagnosis was cervical condyloma and human papillomavirus (HPV) infection.

During the colposcopic examination of the cervix, there was whitening of the raised lesion with application of acetic acid solution. The colposcopist remarked that the lesion, which was near the edge of the transformation zone, "looked just like a wart." No abnormal vascular pattern was noted. Samples of the lesion and two other mildly whitened areas were taken for biopsy, endocervical curettage was performed, and a Papanicolaou smear was repeated.

The Papanicolaou smear showed atypical glandular cells of undetermined significance but suggesting a premalignant process. Findings from the endocervical curettage showed normal cells. Pathologic examination of the wart-like lesion revealed well-differentiated adenocarcinoma, apparently of cervical glandular origin. The depth of invasion of the neoplasm could not be determined because the biopsy specimen was too superficial. The other biopsies were negative for any abnormality.

The patient was referred immediately to a gynecologic oncologist for further examination. After a complete survey for metastases and review of the lesion, the oncologist diagnosed stage IB endocervical adenocarcinoma. After receiving counseling and education about the risks and benefits of radiation and surgical therapies, the patient chose the latter treatment. She underwent a radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymph node dissection. Her surgical and postoperative course was uneventful. Final review of her surgical pathology specimens showed a small amount of residual cervical disease and absence of tumor at the surgical margins and in the lymph nodes.

Six months after surgery, the patient continued to do well on hormone replacement therapy and had no cancer recurrence at frequent follow-up visits.

## Adenocarcinoma

### *History*

According to data from case series before the 1970s, adenocarcinoma made up only 5 to 10 percent of all cervical malignancies.[3,8,11,16-18,21,24,27,28] Thus, in primary care textbooks less attention has been focused on cervical adenocarcinoma than on squamous cell carcinoma.[31] Since the mid-1970s, however, numerous case series from Scandinavia, Europe, the United Kingdom, and the United States have documented an increase in relative incidence, with figures ranging from 10 to 20 percent.[1-30] Some have attributed this increase to the well-documented decrease in invasive squamous cell cancer after the advent of mass screening with Papanicolaou smears in the 1950s.[9,32] Although this association might account for an increasing relative incidence of cervical adenocarcinoma, a number of reports also suggest an increasing absolute incidence for adenocarcinoma.[1,2,6,7,9,21,23,24,29] Referral bias must be considered in series originating from gynecologic oncology centers but cannot account for similar findings in population-based studies.[2,6,21,23]

### *Histopathology*

The histologic classification of cervical adenocarcinomas is controversial, and several schemes exist. Table 1 outlines a simple categorization that is useful for primary care clinicians.[33] Up to 40 percent of adenocarcinomas contain a mixture of subtypes. Endocervical adenocarcinoma often occurs in association with squamous neoplasia, and tumors with invasive elements of both cell types

**Table 1. Simplified Classification of Cervical Carcinoma.**

| | |
|---|---|
| I. | Squamous cell carcinomas |
| II. | Adenocarcinomas |
| | A. Endocervical |
| | B. Endometroid |
| | C. Clear cell |
| | D. Adenoid cystic |
| III. | Undifferentiated carcinomas |

Adapted from Kilgore and Helm.[33]

are categorized as adenosquamous.[34] The most plausible explanation for the coexistence of these cancers is that they arise from a subcolumnar stem or reserve cell that is capable of differentiation to both squamous and glandular epithelium, a theory supported by cell ultrastructural studies of adenocarcinoma in situ (AIS).[34] Because most cases of invasive adenocarcinoma are diagnosed without a preceding diagnosis of AIS, in sharp contrast to the widely acknowledged progression from dysplasia to carcinoma-in-situ to invasive cancer documented for squamous cell neoplasms, there is some question whether AIS represents a precursor lesion to invasive adenocarcinoma.[35] AIS is difficult to diagnose, however, because unlike squamous cell carcinoma in situ, the pathologist cannot use the basement membrane as a readily identifiable boundary for measurement of invasion. Thus, the unclear relationship between AIS and invasive adenocarcinoma could reflect the difficulty in diagnosing AIS rather than a truly independent histologic development.

The clear-cell variant includes neoplasms related to intrauterine exposure to diethylstilbestrol. In utero diethylstilbestrol exposure, although widely recognized as a risk factor by family physicians, accounts for only 2 to 3 percent of cervical adenocarcinomas.[34] The endometroid subtype can be difficult to differentiate from endometrial carcinoma that has spread to the cervix and can be diagnosed only if the endometrium is normal.[34]

### *Epidemiology and Risk Factors*

As stated previously, cervical adenocarcinoma seems to have increased in relative and, perhaps, absolute incidence in the last 20 years. The reasons for the suggested increase in absolute incidence remain unclear. Two case-control studies have reported an association with oral contraceptive use (relative risk approximately 2.0 for 5 to 9 years of use versus no use).[36] One study showed no apparent dose-response relation, however, and no study has adequately addressed potential confounding variables such as sexual behavior. Some of the earliest studies to document an increased incidence of cervical adenocarcinoma, using data from the mid-1970s, showed that women younger than 35 years had experienced the highest increase in disease incidence.[24,27] This cohort included the first generation of women taking oral contraceptive pills, because the pill was first widely prescribed in the early 1960s. In these and subsequent observational studies, an increased incidence of cervical adenocarcinoma was first detected approximately 15 years after the peak ages for oral contraceptive initiation, but in the absence of better case-control studies or any cohort studies, the association remains speculative. Interestingly, the patient described in the present case report was 34 years old, and she had used oral contraceptives for 5 years starting at 19 years, approximately 15 years before her cervical adenocarcinoma was diagnosed.

It is relatively well-established that infection with HPV incurs an increased risk of cervical adenocarcinoma, similar to the association between HPV and squamous cell neoplasms.[34,35,37,38] Nearly all papers report HPV-18 as the predominant subtype found in adenocarcinoma as well as adenocarcinoma in situ. HPV-16 has been isolated less frequently.

Descriptive data on other risk factors for cervical adenocarcinoma are quite sparse. Asian race, obesity, early age at first intercourse, and multiple sexual partners might confer an increased risk of adenocarcinoma.[5,14,20,33-35] Nulliparity and cigarette smoking have not been shown to increase risk for this type of cervical cancer. The studies to date are far from conclusive and often contradictory, however.

### *Diagnosis*

Cervical adenocarcinoma can be more difficult to diagnose than its squamous cell counterpart. Most lesions originate in the endocervical canal and extend into the cervical os, becoming apparent on speculum examination only when they are bulky and cause symptoms.[39] Several studies report an even higher false-negative Papanicolaou smear rate for adenocarcinomas than the 20 to 45 percent rates reported for squamous cell neoplasms.[40] In addition, some experts have suggested that adenocarcinomas account for a larger than expected proportion of so-called rapidly progressive cervical cancers, thus narrowing the window of opportunity for in situ diagnosis.[41,42] In the present case adenocarcinoma was diagnosed by colposcopic biopsy, while the Papanicolaou smear simultaneously showed only atypical glandular cells of uncertain distinction, favoring a premalignant process. Findings on a Papanico-

laou smear done several months earlier were normal. Based on what is known about the natural history of cervical malignancies, the adenocarcinoma was probably present at the time of the normal findings on the Papanicolaou smear, implying a false-negative test. This sequence illustrates why the Papanicolaou smear should not be used to rule out cervical malignancy, especially in the face of unexplained symptoms.

When patients with adenocarcinoma of the cervix are referred for colposcopy, further difficulties can be encountered. No standard colposcopic criteria exist for describing or detecting adenocarcinomas.[43] At least one expert colposcopist lists mistaking adenocarcinoma for a condyloma as a common pitfall in diagnosis.[43] This discovery was especially interesting given the colposcopist's prediagnosis comments pertaining to the appearance of the adenocarcinoma ("like a wart") in this case report. Routine colposcopic biopsy cannot differentiate AIS from invasive adenocarcinoma; at a minimum, cone biopsy must be performed.[34]

Increased recognition of potential symptoms of cervical adenocarcinoma by primary care physicians might allow detection at an early stage. Whereas cervical dysplasia is usually asymptomatic, invasive cervical cancer is often symptomatic. The most common symptoms are irregular vaginal bleeding and bloody discharge, but a nonbloody vaginal discharge may be the only symptom of cervical cancer. By pooling the great number of case series from around the world that reported initial symptoms, it is estimated that the first symptom of 5 to 10 percent of cervical adenocarcinomas is discharge alone.[7,11,17,27,30,41,44-48] Thus, the importance of pursuing the diagnosis of an unexplained vaginal discharge is apparent. Even when findings from naked-eye inspection of the cervix and Papanicolaou smear are unremarkable, colposcopy and endocervical curettage should be considered to help exclude cervical cancer.

### *Staging*

Adenocarcinoma of the uterine cervix is staged using the 1987 revision of the International Federation of Gynecology and Obstetrics (FIGO) classification for cervical cancer (Table 2).[49] Although clinical staging criteria are subjective, the clinical stage is not changed if findings at surgery or during treatment reveal more advanced disease. For stage IV disease, common sites of metastasis are lung, bone, liver, brain, peritoneum, and distant lymph nodes.[50]

**Table 2. International Federation of Gynecology and Obstetrics (FIGO) Classification of Cervical Cancer.**

| Stage | Description |
|---|---|
| 0 | Carcinoma in situ, intraepithelial carcinoma |
| I | Carcinoma strictly confined to cervix (extension to corpus should be disregarded) |
| IA | Microinvasive carcinoma (early stromal invasion) |
| IB | All other cases of stage I; occult cancer should be marked "occ" |
| II | Carcinoma extends beyond cervix but has not extended to the pelvic wall; involves vagina, but not as far as lower third |
| IIA | No obvious parametrial involvement |
| IIB | Obvious parametrial involvement |
| III | Carcinoma has extended to pelvic wall. No cancer-free space between the tumor and the pelvic wall on rectal examination. Tumor involves lower third of vagina. All cases with hydronephrosis or nonfunctioning kidney are included |
| IIIA | No extension to pelvic wall |
| IIIB | Extends to pelvic wall or hydronephrosis or nonfunctioning kidney |
| IV | Carcinoma has extended beyond true pelvis or has clinically involved the mucosa of bladder or rectum |
| IVA | Growth spread to adjacent organs |
| IVB | Growth spread to distant organs |

Adapted from Scott.[49]

Survival for patients with cervical adenocarcinoma, as for those with squamous cell carcinoma, is highly dependent on clinical stage at diagnosis.[11,13,15,16,33,46] The following other factors might help determine prognosis, however: histologic grade, tumor size, depth of invasion, lymph node status, and lymph-vascular space status. Lymph node status is particularly important, with survival from stage I and II lesions decreasing from more than 80 percent to the 10 to 50 percent range at 5 years if nodes are positive.[33] In contrast to squamous cell carcinoma, for which there is an inverse relationship between the number of positive lymph nodes and survival rates, the prognosis for cervical adenocarcinoma is equally worsened whether one node or many nodes are involved.[33]

### *Treatment*

The approach to treatment of adenocarcinoma of the cervix is dependent on clinical staging. For stage I and II disease, radical hysterectomy (including bilateral salpingo-oophorectomy and pelvic lymph node dissection) is the treatment with the highest cure rate and lowest risk of complications.[3,4] Whereas some studies of radiation therapy for stage I and II disease have achieved comparable results, most report lower success rates and higher complication rates. Rectovaginal fistula is particularly troublesome, occurring in up to 20 to 30 percent of patients who receive radiation therapy.[33] Although many authors advocate ovariectomy to eliminate a potential site of metastasis and recurrence, ovarian metastasis is infrequently encountered in patients with stage I disease, and then usually only when there are positive lymph nodes. As a result, some advocate a more selective approach to ovariectomy.[51]

Combination surgical and radiation therapy for stage I and II disease is controversial. Most studies have not found improved survival with combined therapy, and the increase in posttherapy complications with radiation therapy has limited this approach. A possible exception would be bulky stage I and II lesions, in which preoperative radiotherapy could be beneficial.[19,33,34]

Patients with stage III and IV disease fare poorly. Radiotherapy and chemotherapy are generally offered as first-line treatments, with surgery reserved for debulking and palliation.[33]

## Prognosis

The prognosis for adenocarcinoma of the uterine cervix is primarily dependent on the FIGO stage at diagnosis. Overall 5-year survival rates in excess of 80 percent are consistently obtained for surgically treated stage I disease. The 5-year prognosis is uniformly dismal with increasing FIGO stage, however, decreasing to 20 to 30 percent for stage III and approximately 5 percent for stage IV.[35] Many authors report decreased survival for all stages of cervical adenocarcinoma compared with cervical squamous cell carcinoma of equivalent stage, but they used unmatched patients treated at the same or other institutions as a control group, a serious methodologic flaw that limits the strength of their conclusions.[9,11,12,14,16] Overall, it appears that, stage for stage, adenocarcinoma carries roughly the same prognosis as squamous cell carcinoma, but case-matched studies are needed to settle this question.[15] Until that time, the approach to treatment for adenocarcinoma should be the same as for the more common squamous cell carcinoma.[33]

Although recurrence of tumor is most common during the first 2 years after diagnosis, recurrence of adenocarcinoma up to 5 years after definitive therapy is not unusual, in sharp contrast to squamous cell carcinoma for which recurrence after 2 years is rare.[34] Frequent follow-up visits should be continued for at least 48 months after definitive treatment of cervical adenocarcinoma. Tumor can recur locally or at distant sites, but in either case the prognosis is dismal, and almost all patients with recurrent tumor eventually succumb to the disease. Median time from recurrence to death in one review was 23.6 months (range 6 to 71 months), numbers typical of most series.[44] Most patients with recurrence had deeply invasive, large-volume tumors with positive lymph nodes at the time of diagnosis. No good salvage therapy exists.

## Conclusion

Because adenocarcinoma of the cervix has increased in relative and possibly absolute incidence, it is important for family physicians to understand its natural history, particularly as it differs from squamous cell cancer. Using screening Papanicolaou smears, the premalignant phase of adenocarcinoma, AIS, can be more difficult to diagnose than squamous dysplasia or carcinoma in situ preceding invasive squamous cell cancer. This difficulty reflects the tendency of adenocarcinoma to originate within the cervical os, out of reach of a spatula and even a cytologic sampling brush, until it becomes bulky or symptomatic. The lack of a characteristic appearance at colposcopy also contributes to diagnostic difficulty. Despite these pitfalls, early diagnosis is essential if successful treatment is to be initiated. As is squamous cell cancer, adenocarcinoma of the cervix is curable in more than 80 percent of cases, usually by surgery, when detected at stage I. The prognosis for advanced-stage tumors, however, remains dismal no matter which therapy is chosen. Primary care research into better screening and diagnostic tests for this disease is clearly needed.

HPV-18 and, less frequently, HPV-16 infection confer an increased risk for cervical adenocarci-

noma. Less clear is the intriguing assertion that oral contraceptive use might be a risk factor, which could account for the increasing number of cases since the mid-1970s in women younger than 35 years, 15 years after widespread usage of birth control pills began. While this theory is currently supported only by observational, population-based studies, the consistency of reported effect from multiple sites worldwide suggests that case-control and cohort studies in the primary care setting are warranted.

Not only does the case in this report illustrate several of the distinctive features of cervical adenocarcinoma, it also provides another clear message to family physicians: using the Papanicolaou smear to rule out invasive cervical cancer is ill-advised. In the face of unexplained vaginal bleeding or discharge or a grossly visible cervical lesion, the diagnosis of cancer must be entertained even if the results of a Papanicolaou smear are normal. By maintaining a high index of suspicion for cervical cancer in the face of suggestive symptoms, an early diagnosis and an excellent prognosis for the patient can be achieved.

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