Histologic and Clinical Characteristics Associated with Rapidly Progressive Invasive Cervical Cancer: A Preliminary Report from the Yale Cancer Control Research Unit

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Histologic and clinical characteristics associated with rapidly progressive invasive cervical cancer are presented in this preliminary report from a population-based study involving all patients in Connecticut diagnosed with cervical cancer from March 1, 1985. Rapidly progressive invasive cervical cancer, i.e., invasive cancer diagnosed within three years of a true negative Pap smear, is more likely to occur in younger women with high annual incomes (61 percent > $40,000) who report a greater frequency of benign gynecologic conditions (uterine leiomyomata, vaginitis) compared to a control cervical cancer group. These preliminary data suggest that as many as 35 percent of the rapidly progressive cervical cancers are likely to be adenocarcinomas. Because they are mostly endocervical in origin, they may not be detected cytologically if scrapers or cotton swabs are used to sample the endocervical canal. New cytologic screening techniques using brushes may identify these lesions earlier and should routinely be employed in cytologic screening for cervical neoplasia. The difficulty in early detection of this form of the disease requires that physicians rapidly assess patients with unexplained pelvic and lower abdominal pain, vaginal discharge, or abnormal vaginal bleeding since early recognition is the only chance for cure. Further analyses of this population of women will be made to identify additional risk factors when the study data are complete.

INTRODUCTION

Cervical cancer is the only cancer for which there has been long-term and widespread screening. The Papanicolaou (Pap) test, a cytologic method used to detect precursor lesions of the cervix, has contributed to the decreasing incidence and mortality rates. While it has been assumed that the natural history of cervical cancer has a long pre-clinical phase, data have begun to accumulate which suggest that a significant portion of invasive cervical cancer cases progress rapidly and, therefore, cannot be prevented with the existing early detection programs [1–3]. More recent data indicate that the percentage of such rapidly developing cases may be as high as 25

Abbreviations: CIS: carcinoma in situ  F.I.G.O.: International Federation of Gynecologists and Obstetricians  HPV: human papilloma virus  
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percent to 33 percent [4–7]. The interval from the last negative cytological finding to a
diagnosis of invasive cancer varied between two and five years in the latter studies. So
far, no distinctive characteristics have been reported to single out these women, except
in a Yale University report on clinical management of rapidly progressive invasive
cervical cancer patients, where 88 percent were found to be less than 40 years old [8].
A major weakness in these studies is the lack of verification of the “negative smear” by
a second cytopathologist, which leads to the inclusion of false-negative cases with the
rapidly progressive invasive cervical cancer group.

The purpose of this paper is to present preliminary data from a population-based
study where Pap smear data has been verified by experienced cytopathologists in order
to present histologic findings and clinical symptomatology associated with rapidly
progressive cervical cancer. It is based on data collected for a cancer control project
aiming to improve early detection methods for cervical cancer through interventions
developed from the study results [9]. It is hoped that this preliminary report will serve
as part of a statewide cervical cancer intervention since the report is alerting physicians
to the difficulties of detecting the pre-invasive stage of adenocarcinoma using the Pap
test.

MATERIALS AND METHODS

This investigation is being conducted by the Cancer Control Research Unit of
the Department of Epidemiology and Public Health at Yale University School of
Medicine. The current project is enrolling all incident cases of invasive cervical cancer
diagnosed in Connecticut between March 1, 1985, and March 1, 1990. Information on
eligible patients is collected with a pre-tested, structured questionnaire administered
by a telephone interview. The study to date has completed 373 interviews, and
cytologic review has been completed for 223 patients.

Cytology slides are collected and reviewed for all invasive cancer cases. Based on
information obtained during the interview, all physicians who may have performed Pap
tests on the patient in the past are contacted. Subsequently, cytology slides are
requested from the various laboratories and reviewed by the pathologists. The medical
review committee studies all reports from cervical biopsies and/or hysterectomies and
all reports from available Pap tests. Each case is then classified by the medical review
committee [consisting of a gynecologic oncologist (PES), a cytopathologist (DML),
and an epidemiologist (JWM)] into one of four categories that identify the reason for
failure. These categories are: (1) not reached by screening, (2) misread Pap smears, (3)
detected by screening test but not adequately treated, and (4) rapidly progressive
disease not detected through routine screening procedures.

Rapidly progressive invasive cervical cancer is defined as cervical cancer occurring
within three years of the last true negative Pap smear. The three-year interval was
selected based on the American Cancer Society’s recommendation for triennial Pap
smear screening. Discrepancies between original Pap smear readings and those of the
review cytopathologists are resolved by having an additional expert cytopathologist
(MM) review the slides. Thirty-one cases have been classified as rapidly progressive to
date. Patients in the first three categories of the classification scheme have been
grouped together and form the cervical cancer comparison group, i.e., patients with
“slowly developing” cervical cancers. This comparison group includes 166 cases. It
should be pointed out that the comparison group may include some women who would
be classified as rapidly progressive had they been screened with a Pap smear; this
RAPIDLY PROGRESSIVE CERVICAL CANCER

TABLE 1
Distribution of Age and Income Among Patients with Rapidly Progressive Invasive Cervical Cancer and Two Comparison Groups

| Factors       | % Rapidly Progressive Cervical Cancer n = 31 | % Invasive Cervical Cancer n = 166 | % In Situ Cervical Cancer n = 76 |
|---------------|-------------------------------------------|----------------------------------|----------------------------------|
| Age at Diagnosis |                                             |                                  |                                  |
| <35 years     | 29                                         | 27                               | 23                               |
| 35–44         | 33                                         | 21                               | 23                               |
| 45–54         | 32                                         | 18                               | 24                               |
| 55–64         | 3                                          | 18                               | 18                               |
| 65+ years     | 3                                          | 16                               | 12                               |
| Income        |                                            |                                  |                                  |
| Less than $40,000 | 29                                         | 73                               | 68                               |
| $40,000 or more | 61                                         | 18                               | 24                               |
| Refused information | 10                                         | 9                                | 8                                |

The possibility may lead to a more conservative interpretation of the results. An additional 76 patients with carcinoma in situ (CIS) of the cervix have been included as a second comparison group. These were group-matched for age within a five-year interval with the 1985 and 1986 cases.

International Federation of Gynecologists and Obstetricians (F.I.G.O.) staging was available for 25 of 31 patients with rapidly progressive invasive cervical cancer. Twenty-four were F.I.G.O. stage IB and one stage IAii. Thus, all of the cancers staged were clinically confined to the cervix. F.I.G.O. staging for the control group of cervical cancers is not presently available. Among the rapidly progressive cases, the interval from the last normal Pap smear to the time of diagnosis was six months or less in five patients, 7 to 12 months in ten, 13 to 18 months in ten, 19 to 24 months in two, 25 to 30 months in three patients, and 31 to 36 months in one patient.

Since the comparison groups in this case-control analysis may be subject to the same risk factors as the cases, these risk factors are evaluated with respect to their “relative influence” on a woman developing rapidly progressive invasive cervical cancer. Because the data presented here are preliminary, analysis was restricted to contingency tables, and statistical significance is not being reported.

RESULTS

Preliminary analysis of some risk factors associated with cervical cancer reveals that rapidly progressive invasive cervical cancer occurs most often in a younger population, since 93 percent was diagnosed in women under age 54 versus 66 percent of the control group of invasive cancer patients and 70 percent of the CIS group (Table 1). Sixty-one percent of women with the rapidly progressive invasive cervical cancer have an annual family income of $40,000 versus 18 percent and 23 percent, respectively, for the two control groups.

Patients in the rapidly progressive cervical cancer group are more likely to report ever having had gynecologic disorders, specifically uterine leiomyomata and vaginitis, than the two comparison groups (Table 2). The rest of the conditions are reported by very few patients in all of the groups.
TABLE 2
Distribution of Previous Gynecologic Disorders and Symptoms Associated with Cervical Cancer Among Rapidly Progressive Cases and Two Comparison Groups

|                              | % Rapidly Progressive Cervical Cancer n = 31 | % Invasive Cervical Cancer n = 166 | % In Situ Cervical Cancer n = 76 |
|------------------------------|---------------------------------------------|-----------------------------------|---------------------------------|
| Previous Gynecologic Disorders |                                             |                                   |                                 |
| Vaginitis                    | 58                                          | 36                                | 46                              |
| Uterine leiomyoma            | 23                                          | 7                                 | 9                               |
| Endometriosis                | 6                                           | 1                                 | 12                              |
| Pelvic inflammatory disease   | 3                                           | 5                                 | 3                               |
| Ovarian cysts                | 3                                           | 8                                 | 9                               |
| Genital warts                | 3                                           | 2                                 | 8                               |
| Sexually transmitted disease | 3                                           | 4                                 | 8                               |
| Herpes                       | —                                           | 1                                 | 5                               |
| Symptoms Associated with Cervical Cancer |                                 |                                   |                                 |
| Vaginal bleeding             | 57                                          | 64                                | 20                              |
| Spotting after intercourse   | 23                                          | 24                                | 13                              |
| Abdominal pain               | 26                                          | 42                                | 26                              |
| Vaginal discharge            | 26                                          | 40                                | 25                              |
| Weight loss                  | 6                                           | 16                                | 4                               |
| Difficulty urinating         | 3                                           | 12                                | 8                               |

Among the symptoms most frequently associated with cervical cancer, abnormal vaginal bleeding is equally reported by the rapidly progressive cases (57 percent) and the control invasive cancer group (64 percent). Pelvic or lower abdominal pain and vaginal discharge is reported less frequently by the patients with rapidly progressive cancer. Additional symptoms of weight loss and difficulty urinating are not common among the cases. As expected, patients with CIS are reporting a substantially lower frequency of symptoms than either of the invasive cancer groups.

Substantial differences in histology (Table 3) are being observed between the two groups of invasive cancer patients. Thirty-five percent of women with rapidly progressive cervical cancer are diagnosed with adenocarcinoma, whereas only 11 percent of the invasive comparison group has adenocarcinoma. An additional 10 percent of the rapidly progressive cases have adenosquamous carcinoma versus only 3 percent among the invasive comparison group.

DISCUSSION

The identification of risk factors and characteristics associated with rapidly progressive invasive cervical cancer is of the utmost importance, as this disease is almost invariably fatal once it has spread beyond the cervix. Experience at this institution suggests that this cancer is not responsive to radiation therapy, thus limiting effective treatment to radical cancer surgery [8].

The preliminary data presented in this population-based series substantiate our previous impression that rapidly progressive invasive cervical cancer is a disease of younger women, and, because it is symptomatic, it is identified most often as stage I cancer [8]. Surprisingly, these data suggest that it is a disease of middle- and upper-class women, with two-thirds having an annual income greater than $40,000. With regard to benign gynecologic disorders, more patients with rapidly progressive
cervical cancer are reporting ever having had uterine leiomyomata and vaginitis. It appears that at least some of the diagnoses of cervical cancer were missed or delayed because of the negative Pap smears, leading physicians to ascribe abnormal vaginal bleeding to uterine leiomyomata and vaginal discharge to nonspecific vaginitis instead of evaluating the endocervical canal.

Histologic review of the cases showed that 35 percent of rapidly progressive cervical cancer patients had adenocarcinoma of the endocervix. This histologic type appears not to exfoliate cells as well as squamous carcinoma. Cervical adenocarcinomas are less likely to be identified by Pap smear screening than squamous cell cancers of the exocervix, and the patient's symptoms are what lead the physician to evaluate the endocervical canal [10]. Perhaps squamous carcinomas that are found to be rapidly progressing also initiate in the endocervix and either are inadequately sampled or are less likely to exfoliate cells that may be identified by routine cytology techniques. Thus the concept of rapid progression may reflect inadequate or incomplete cytologic sampling of the endocervix rather than true virulence.

Squamous cell carcinomas are believed to arise in the endocervical canal from the subcolumnar reserve cells, which form a single layer of cuboidal epithelium [11]. These reserve cells proliferate and stratify into squamous epithelium, the process being known as squamous metaplasia. The human papilloma virus (HPV) has been implicated in the genesis of cervical squamous cancer, and recent in situ DNA hybridization studies suggest that HPV type 18 is the most common subtype found in adenocarcinomas of the cervix [12], whereas the more common squamous carcinomas are most often associated with HPV type 16.

From a practical standpoint, our preliminary results suggest that many patients may have had a technically adequate Pap smear, i.e., both squamous and columnar cells are present, but may not have had sufficient sampling of the endocervical epithelium to establish the correct diagnosis. Cotton swabs are still routinely used by many Connecticut physicians to obtain cytologic material from the endocervical canal. A much better sampling technique is now available, using the cytobrush, which has been demonstrated to lower the number of inadequate smears and false-negative cytology [13–15].

When patient accrual is completed, detailed analysis of the final data will be done in order to identify risk factors and patients' characteristics associated with rapidly progressive invasive cervical cancer and to verify the preliminary results reported here. At this time, however, early results indicate that rapidly progressive invasive cervical cancer is a disease of women who can afford and do utilize private medical care.

### TABLE 3
Histologic Characteristics of Invasive Cervical Cancer Among Rapidly Progressive and All Other Cervical Cancer Cases

| Tumor Type       | % Rapidly Progressive Cervical Cancer | % Invasive Cervical Cancer |
|------------------|-------------------------------------|---------------------------|
| Squamous Cell    | 55                                   | 86                        |
| Adenocarcinoma   | 35                                   | 11                        |
| Adenosquamous    | 10                                   | 3                         |

Rapidly Progressing Tumor demonstrated because adenocarcinomas are much less likely to be identified by Pap smear screening than squamous cell cancers of the exocervix, and the patient's symptoms are what lead the physician to evaluate the endocervical canal [10]. Perhaps squamous carcinomas that are found to be rapidly progressing also initiate in the endocervix and either are inadequately sampled or are less likely to exfoliate cells that may be identified by routine cytology techniques. Thus the concept of rapid progression may reflect inadequate or incomplete cytologic sampling of the endocervix rather than true virulence.

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Physicians should routinely employ the cytobrush technique rather than the cotton swab to obtain endocervical cytology specimens. A negative Pap smear in no way guarantees that an endocervical carcinoma is absent. One should not be misled into believing that abnormal vaginal bleeding is due to a uterine leiomyoma or that a discharge is due to a nonspecific vaginitis because a Pap smear is negative. Liberal use of endocervix biopsies is mandatory in the presence of unexplained lower abdominal pain, vaginal discharge, or vaginal bleeding. Early recognition of rapidly progressive invasive cervical cancer is the only hope a woman has for successful treatment of this disease.

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