Pap Smear Screening and Invasive Cervical Cancer

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Possible failures of Pap smear screening were assessed among 63 cases of invasive cervical cancer that occurred in a group practice population between 1965 and 1975. Review of medical records revealed 33 (53 percent) cases with no history of Pap smears within two years prior to diagnosis. Among the 30 patients with recent Pap screening, 11 (17 percent) had negative smears; these could only be explained as false negatives or unusually rapid progression of disease. The remaining 19 (30 percent) had abnormal smear results, a number of whom received suboptimal follow-up care. Similar experiences have been reported from several other health care settings. Implications for preventive practices are discussed.

Invasive cervical cancer is theoretically a preventable disease if cytologic changes are detected early and appropriate treatment is undertaken. Since the early 1950s clinicians have employed the Pap smear for detecting cervical cancer at a pre-invasive state, and subsequent treatment by conization, cryotherapy, or hysterectomy has yielded considerable success in preventing progression to invasive disease.[1,2] In spite of this success, thousands of new cases of invasive cervical cancer occur each year in the United States. Numerous authors have suggested that either maldistribution of Pap screening services or high rates of false negative tests are at fault.[3-6]

As a direct means of explaining why cases of a preventable chronic disease such as invasive cancer of the cervix were not prevented, Rutstein et al[7] proposed a method that focuses on the cases themselves. Given a preventive model for the disease, the past health care history in each case is examined to determine at what point the model may have failed to apply.

The following preventive model for invasive cancer of the cervix has been used in this study:

1. Cytologic progression from normal to invasive carcinoma usually occurs over a period of at least two years and passes through intermediate stages including cancer in situ

2. Adult women are screened at least every two years for detection of cytologic evidence of cancer

3. No false negatives occur in the screening tests

4. Inadequate, atypical, suspicious, or positive screening tests receive appropriate follow-up screening or treatment

A series of cases of invasive cancer of the cervix occurring in a general population have been

systematically investigated to determine to what extent failure of each component of this model contributed to the continuing occurrence of the disease.

Methods

The study was conducted within the Oregon Region Kaiser-Permanente Medical Care Program, a federally certified health maintenance organization that currently enrolls approximately 215,000 persons in the Portland, Oregon, metropolitan area. This population consists of 15 to 20 percent of the metropolitan population and is broadly representative of the community in demographic terms.[8] Health services are provided by a group of over 200 physicians, most of whom represent the primary care specialties. Personal preventive services, such as Pap smears, are provided as part of regular medical care. Pap smears are read by the Kaiser cytopathology laboratory and are reported as negative, atypia-benign (including inflammation, metaplasia, mild and moderate dysplasia), atypia-suspicious, malignant, or inadequate. Negative test reports are filed directly into the patients' medical records; all other results are reported directly to the clinician. Follow-up is recommended within six months for mild dysplasia, three months for moderate dysplasia, and immediately for atypia-suspicious, malignant, or inadequate test results.

All patients with invasive cancer of the cervix diagnosed between 1965 and 1975 were identified by a review of the Kaiser cancer registry. During this period an average of 8 new cases occurred per year, with crude annual incidence rates declining from 18 cases per 100,000 population in 1965 to 12 cases per 100,000 in 1975. Those who had been enrolled in the Kaiser-Permanente program for at least two years prior to diagnosis were included in the study. Sixty-three cases met these criteria. Patients' median age was 52 years, with a range of 24 to 85 years. Data concerning the patients' index visit (contact which led to the diagnosis) and all prior health service visits (clinic, emergency room, hospitalizations) during the two years preceding diagnosis were obtained from a review of the patients' medical records. The presence of any gynecologic symptoms and the cytologic diagnosis from all Pap smears performed were specifically noted.

Table 1. Cases with No Pap Screening in Prior Two Years (n=33)	
	Number of Cases
Number of Health Service Visits	
0	3
1-3	14
4-6	4
7 or more	12
Presenting Gynecologic Symptoms	
Prior to diagnosis	4
At diagnosis	16
Disease Stage	
Ia	6
Ib	6
II	10
III	10
IV	1

Results

Thirty-three patients, representing 52 percent of the cases, received no Pap screening in the two years preceding diagnosis and are summarized in Table 1. Their median age was 58 years, with a range of 28 to 85 years. All but three had made at least one health service visit during the two years prior to diagnosis but had not received Pap screening. Gynecologic symptoms were rarely present during these visits, although they developed in over one half the cases by the time of diagnosis. These patients also tended to have advanced stages (II and above) of disease at diagnosis.

The remaining 30 patients had received at least one Pap smear during the two-year period before diagnosis. Table 2 summarizes the Pap smear and health service utilization data for those 11 patients whose Pap smears were reported as negative. Median age was 52 years, with a range of 28 to 83 years. All of these patients had multiple health service visits during the two-year period, and almost one half complained of some gynecologic symptoms before their cancer was diagnosed. Three of these patients were diagnosed with advanced stage disease. Five patients, including two of those with advanced disease, had received negative Pap smears within the 12 months prior to

Table 2. Cases with All Negative Pap Smears in Prior Two Years (n=11)	
	Number of Cases
Number of Months Since Last Pap Smear	
1-6	1
7-12	4
13-18	4
19-24	2
Number of Health Service Visits	
0	0
1-3	3
4-6	1
7 or more	7
Presenting Gynecologic Symptoms	
Prior to diagnosis	5
At diagnosis	6
Disease Stage	
Ia	3
Ib	5
II	1
III	1
IV	1

Table 3. Cases with Abnormal Pap Smears in Prior Two Years (n=19)	
	Number of Cases
Prior Pap Smear Result	
Atypia (suspicious)	3
Atypia (benign)	13
Inadequate	1
"Negative" (see text)	2
Number of Months Since Last Pap Smear	
1-6	5
7-12	5
13-18	6
19-24	3
Number of Health Service Visits	
0	0
1-3	1
4-6	2
7 or more	16
Presenting Gynecologic Symptoms	
Prior to diagnosis	4
At diagnosis	11
Disease Stage	
Ia	11
Ib	5
II	2
III	1
IV	0

their index visit, suggesting that falsely negative tests likely occurred. In six cases the interval between the last negative Pap smear and the index visit at diagnosis exceeded 12 months. Five of these cases were classified as stage Ia or Ib and may have represented cases in which full progression from noninvasive early disease to invasive cancer was unusually rapid.

The 19 cases summarized in Table 3 represent the final group of patients who received Pap screening and whose Pap smears were abnormal prior to the actual diagnosis. This group was somewhat younger, with a median age of 39 years and a range of 24 to 78 years. The specific abnormality on their prior Pap screening ranged from simply being "inadequate" for cytologic interpretation in one case (which was repeated one month later leading to the diagnosis) to three cases for which Pap smears were read as atypia-suspicious. Eight patients had received more than one Pap smear during the two-year period, including two patients whose most recent tests were reported as

negative. One of these patients had received two "inadequate" Pap smears five and six months prior to the negative result; the other patient had an atypia-suspicious smear four months preceding the negative test. Thirteen of these 19 cases had multiple health service visits during the interval following an abnormal test result and before the index visit, suggesting that earlier follow-up of all inadequate or atypical smears during these visits may have led to earlier diagnosis. Intervals between last Pap smear and diagnosis ranged from 1 to 24 months, with intervals of over 12 months occurring in nearly one half the cases. Because the atypia-benign classification includes a variety of cytologic interpretations (discussed under Methods), it is difficult to evaluate whether their follow-up intervals were appropriate. However, if

any of these patients' smears demonstrated even mild dysplasia, then more prompt follow-up was certainly indicated.

Discussion

This analysis identifies points at which the proposed preventive model for carcinoma of the cervix may have failed to apply in the population under study. These findings raise several points for further discussion. First, what were the circumstances under which the components of the preventive model failed, and what corrective measures might be indicated? Second, how does this experience compare with that of other populations, and in turn, what general corrective measures in delivery of preventive health services might be indicated to further minimize the occurrence of cancer of the cervix?

Failure to receive routine Pap screening, the most obvious point at which the preventive model might be expected to fail, was found in approximately one half of the invasive cases. Most of these women had had multiple medical care contacts, primarily with internists or gynecologists during the two years prior to diagnosis, and gynecologic symptoms were rarely noted at these visits. Clearly the failure to receive Pap smears cannot be attributed to lack of access to health services; rather, the evidence points to a lack of effective performance on the part of provider or patient in utilizing the appropriate preventive service, ie, the Pap smear. The absence of any gynecologic symptoms as an incentive to such performance underscores that effective preventive behavior must be based upon knowledge of risk of incurring disease rather than presence of any overt manifestations.

The finding that 30 of the 63 cases occurred in women who had received one or more recent Pap smears focuses attention on several other aspects of the preventive model. First is the potential for patient and provider to have been mistakenly reassured by false-negative test results. This explanation seems to apply to some of the 11 cases with a history of negative Pap smears within the two years prior to diagnosis. False-negative tests may be attributed to inadequate cytologic sampling or interpretation, a subject well reviewed by Briggs.[6]

Alternatively, false-negative results could arise from inflammatory change or from necrosis of a tumor mass. Proper diagnosis of invasive cervical cancer ultimately depends upon biopsy, not cytology; hence, regardless of Pap screening, any suspicious cervical lesion warrants appropriate evaluation, including colposcopic examination with directed biopsy or conization.

Some of the cases of invasive disease that developed within one to two years of negative Pap screening may also have represented instances of unusually rapid progression of the disease process. Such cases would constitute an exception to the premise of the preventive model that all invasive cervical cancer is preceded by a gradual progression of identifiable changes over a period of years. Figge et al[9] have reported similar cases of invasive disease occurring despite recent negative Pap smears. These cases, which would benefit little from traditional annual or biennial Pap screening, appear to represent a relatively small proportion of all cases.

A final area of concern with the preventive model rests with the assurance of appropriate follow-up for abnormal Pap smears. As previously noted, it appears probable that at least some of the patients with recent abnormal Pap smears (Table 3) did not receive prompt follow-up. In several such cases more than a year elapsed before another smear was taken, despite these patients' utilization of other ambulatory services during the intervening period. Furthermore, the follow-up periods occurring in patients with atypia-suspicious cytology reported in the last smear prior to diagnosis were 3, 5, and 16 months; thus all three exceed the recommended immediate follow-up. Clearly, the efficiency of Pap screening in the prevention of invasive cancer depends upon prompt retesting or treatment for those patients with abnormal cytology. The presence of atypical cells may place the patient in a much higher risk category for developing cancer. Stern[10] observed progression to malignant changes among 4.9 percent of patients with previously demonstrated dysplasia; this represented a rate 1,200 times that for patients with negative smears.

In summary, in the population and setting under study, failure to obtain periodic Pap screening accounted for approximately one half of the invasive cancer cases, whereas 17 percent of cases occurred as a result of false-negative tests or unusu-

ally rapid disease progression, and 30 percent were attributable to insufficient follow-up of abnormal Pap smears.

Observations on invasive cervical cancer from three other settings are comparable with the findings reported here. MacGregor et al[11] reviewed the past medical care of 30 invasive cases identified in 1968-69 in Aberdeen, a Scottish community in which a comprehensive cervical cytology program was established in 1960. They found that 22 cases (73 percent) occurred in women who had not had recent Pap smears. Responsibility for these failures was attributed partly to physicians who had not incorporated the comprehensive cervical cytology program into their practices and partly to patients who did not come for Pap screening despite multiple invitations to do so. Of the eight cases with history of recent Pap smears (27 percent), four had abnormal findings at the time of initial screening, and invasive cancer was confirmed on prompt follow-up evaluation; the other four were attributed to false-negative tests.

Nelson and Choi[12] reviewed several hundred cases of invasive cancer that occurred in Manitoba (Canada) following the introduction of a screening program in 1963. Approximately 60 percent of these cases had not been previously screened. One half of the remaining cases had a history of a recent negative Pap smear and were thought to be primarily attributable to false-negative testing, and one half had a history of abnormal test results without adequate follow-up evaluation.

Fruchter et al[13] reviewed the prior Pap screening and medical care received by 97 women who developed invasive cervical cancer in a medically indigent population in New York City. Approximately one half had received no recent Pap smears despite their rather extensive utilization of ambulatory care services.

Systematic review of invasive cervical cancer cases in these different settings has shown that failure to receive Pap screening was consistently the most common specific shortcoming in the preventive model. However, in each setting sizeable proportions of cases were found to be associated with either inadequate follow-up of abnormal Pap smears or false-negative tests. The value of such studies lies in their capacity to define potentially correctable deficiencies in the preventive model and thereby provide a rational basis for allocating resources to further prevent the disease in question. While applied specifically to the problem of cervical cancer in this study, this approach may be equally applicable to other preventable chronic diseases such as stroke and breast cancer.[14,15]

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