Cervical Cancer in Women With Comprehensive Health Care Access: Attributable Factors in the Screening Process

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Background: **Invasive cervical cancer is highly preventable, yet it continues to occur, even among women who have access to cancer screening and treatment services. To reduce cervical cancer among such women, reasons for its occurrence must be better understood. We examined factors associated with the diagnosis of cervical cancer among women enrolled in health plans.** ***Methods:*** **We identified all cases of invasive cervical cancer (*n* = 833) diagnosed from January 1, 1995, through December 31, 2000, among women who were long-term members of seven prepaid comprehensive health plans and reviewed each woman's medical records for the 3 years prior to her cancer diagnosis. Women were classified into one of three categories based on Pap test histories 4–36 months before diagnosis: failure to screen with a Pap test, failure in detection by a Pap test, or failure in follow-up of an abnormal test result.** ***Results:*** **The majority of cases (*n* = 464; 56%) were in women who had no Pap tests during the period 4–36 months prior to diagnosis. Of the remaining cases, 263 (32%) were attributed to Pap test detection failure and 106 (13%) to follow-up failure. Being older (odds ratio [OR] = 6.48, 95% confidence interval [CI] = 3.89 to 10.79) or living in an area of higher poverty (OR = 1.72, 95% CI = 1.11 to 2.67) or having a lower education level (OR= 1.52; 95% CI = 1.07 to 2.16) was associated with the likelihood of being assigned to the failure to screen category versus either of the other two categories. A total of 375 (81%) of the 464 patients who had not had Pap screening had had at least one outpatient visit 4–36 months prior to cancer diagnosis. The cancer diagnostic process was triggered by a routine screening examination in 44% of patients, whereas 53% of the patients presented with symptoms consistent with cervical cancer; the remaining 3% were identified fortuitously during the course of receiving noncervical care.** ***Conclusions:*** **To reduce the incidence of invasive cervical cancer among women with access to screening and treatment, Pap screening adherence should be increased. In addition, strategies to improve the accuracy of Pap screening could afford earlier detection of cervical cancer. [J Natl Cancer Inst 2005;97:675–83]**

Cervical cancer is one of the best understood neoplasms, given its well-known viral etiology. It is also one of the most preventable human cancers, because of its slow progression, cytologically identifiable precursors, and effective treatments. Papanicolaou (Pap) cervical cytology screening has helped to reduce cervical cancer rates dramatically through the detection of premalignant lesions *(1,2)*. From 1975 to 2000, the Surveillance, Epidemiology, and End Results (SEER)-based age-adjusted incidence rate of invasive cervical cancer in the United States decreased from 14.8 to 7.6 per 100 000 women/year *(3)*. In the past decade, new technologies, including liquid-based monolayer cytology and computer-assisted reading of Pap slides, have been introduced to improve the sensitivity and specificity of cervical cytology *(4)*. Despite these advances in secondary prevention of cervical cancer, in 2000 more than 12 000 new cases of cervical cancer were diagnosed and more than 4000 women died from the disease in the United States *(3)*.

A lack of Pap screening, which often results from a lack of health care access, has been implicated universally as the most common attributable factor in the development of invasive cervical cancer *(5–9)*. Two studies have reported that a lack of Pap screening was also the most common attributable factor in the development of cervical cancer among women who had access to health care *(10,11)*. A population-based Canadian study reported that 46% of the women who were diagnosed with cervical cancer had not had a Pap test within the 3 years prior to diagnosis *(11)*; a study of a large U.S. prepaid, comprehensive health plan reported that 53% of women who were diagnosed with cervical cancer had not had a Pap test within the 3 years prior to diagnosis *(10)*. Several studies found that older women who were diagnosed with cervical cancer were less likely to have been screened by Pap testing than younger women diagnosed with cervical cancer *(5,10,11)*. The U.S. study *(10)* also found that nonwhite women who were diagnosed with cervical cancer were statistically significantly less likely to have been screened by Pap testing than white, non-Hispanic women who were diagnosed with cervical cancer.

Two studies *(10,11)* have identified factors that that are associated with the development of cervical cancer in women who did receive Pap screening. These factors include inadequate follow-up of abnormalities detected by a Pap test and the failure of the Pap test to detect an abnormality. In each of these studies, a small proportion (<10%) of the cervical cancer cases was ascribed to failure during follow-up on the basis of a review of the patients'

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medical records preceding cancer diagnosis *(10,11)*. Both studies reported that nearly one-third of the women who were diagnosed with cervical cancer had one or more negative Pap tests within the 3 years prior to their diagnosis. One study *(11)*, a population-based investigation among women who had access to health care, included a cytology review of Pap test results that were reported as normal prior to the cancer diagnosis.

Ideally, all cervical cancers should be detected as premalignant lesions and treated before they progress to invasive cervical cancer. Therefore, the occurrence of an invasive cervical cancer represents a failure in the cancer screening process. We recently proposed a conceptual framework for evaluating the quality of cancer care across the continuum, from risk assessment to cancer screening, detection, diagnosis, treatment, and surveillance through end-of-life care *(12)*. This model was used in a study that examined factors associated with failures in the breast cancer screening process *(13)*.

Here we have applied this framework to an investigation of factors associated with invasive cervical cancers diagnosed in women who were members of one of seven comprehensive, prepaid health plans. We evaluated the detailed medical histories of a large and diverse population of women who developed cervical cancer despite having long-term access to comprehensive cervical cancer screening and treatment. Our goals were to identify and explore screening process failures attributable to a cervical cancer occurrence, and to elucidate factors associated with screening failure.

This study is a component of the multicenter Detection of Early Tumors Enables Cancer Therapy (DETECT) Study. The DETECT Study is an effort of the Cancer Research Network, a collaboration of comprehensive health plans funded by the National Cancer Institute to increase the effectiveness of preventive, curative, and supportive cancer interventions *(14)*.

Subjects and Methods

Setting and Study Subjects

Cervical cancer cases were identified among members of seven prepaid comprehensive health plans, which together serve more than 8 million members: Kaiser Permanente Medical Care Program of Northern California (KPNC; Oakland, CA), Kaiser Permanente Medical Care Program of Southern California (KPSC; Pasedena, CA), Kaiser Permanente Northwest (KPNW; Portland, OR), Kaiser Permanente Hawaii (KPHI; Honolulu, HI), Kaiser Permanente of Colorado (KPCO; Denver, CO), Group Health Cooperative (GHC; Seattle, WA), and Henry Ford Health System/Henry Ford Medical Group (HFHS; Detroit, MI). We used institutional cancer registries that were maintained at each site to identify all invasive cervical cancer cases (ICD-O codes C53.0–C53.9) diagnosed from January 1, 1995, through December 31, 2000. Five of the seven sites selected for this study (KPNC, KPSC, KPHI, GHC, and HFHS) maintain tumor registries that contribute to the National Cancer Institute's SEER Program. We included only cervical cancer cases diagnosed among women who were health plan members on the cancer diagnosis date and were enrolled in the health plan for at least 33 of the 36 months prior to diagnosis.

The Pap screening rates among these health plans are high (80%–86% of women aged 21–64 years had been screened from 1998 through 2000), and the cervical cancer rates among the health plan members are relatively low (i.e., 4.2–7.4 cases per 100 000 women compared with the U.S. rate of 9.5 cases per 100 000 women in the year 2000) *(15)*. Nevertheless, nearly 300 cases of invasive cervical cancer were diagnosed annually from 1995 through 2000 among the seven plans.

This study was approved by the human subjects review committee of each participating health plan.

Time Periods

The cervical cancer diagnosis date, which was determined from tumor registry records, was the reference point for all time periods examined in this study. For 94% of the women diagnosed with invasive cervical cancer, the cancer diagnosis process began with an abnormal Pap or other test result received within the 4 months prior to diagnosis. Therefore, we defined the 4-month period prior to the diagnosis date as the "diagnostic period." To assign an attributable failure in the screening process to each woman, we studied the period from 4 to 36 months preceding diagnosis. We defined this interval as the "potential intervention period," during which a change in the screening process might have led to an earlier cancer diagnosis or detection of the cancer at the preinvasive stage. If the earliest visit during the 4 to 36 months prior to diagnosis was a follow-up visit for a cervical abnormality, we extended the potential intervention period back in time to the visit that generated the follow-up visit (e.g., a visit during which a routine Pap test was performed that had an abnormal result). The 12-month period following the diagnosis date was considered the postdiagnosis period; we used tumor type information that was collected during this period.

Data Collection and Creation of Analytic Variables

Outpatient medical charts. Using standardized medical record abstraction forms, we collected information regarding all gynecologic procedures the patient had undergone and her history of cervical disease, including the date of the clinic visit, the reason for the visit, any reported symptoms of cervical cancer, test results, physician recommendations, and evidence of patient noncompliance, from outpatient medical records that covered the 3 years prior to diagnosis. Pregnancy history was also collected.

Potential symptoms of cervical cancer were defined as abnormal (i.e., nonmenstrual) bleeding, pain or bleeding with intercourse, and pelvic pain. Evidence of patient noncompliance was defined as an explicit notation in the patient's medical chart stating that she had refused to follow the advice of her health care provider (e.g., regarding screening or further diagnostic testing). Missed appointments alone were not considered to be evidence of patient noncompliance. Most Pap smear results were reported using the standard diagnostic categories of the Bethesda System *(16)*. Pap smear results that were not reported using the Bethesda System were translated into Bethesda System categories by medical records abstractors who used keywords mapped to Bethesda System categories. Cervical pathology results produced during the 12-month postdiagnosis period were also recorded to ensure complete tumor histology data. Tumor cell type was determined from histology reports and classified as squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or other (e.g., small-cell carcinoma, glassy cell carcinoma, or adenosarcoma). Study files included photocopies of all pertinent cytology and

histology reports. We collected Pap test history from the time period prior to the study period (i.e., more than 3 years prior to diagnosis) when available. One woman had a prior history of invasive cervical cancer and was included in this study.

Trained medical record abstractors at each site completed the chart abstraction. All abstraction forms were then reviewed and coded by the project coordinator and principal investigator (MMM) at the Coordinating Center (KPNC). Data were double-entered at a single facility (KPNC). Quality-control measures included extensive training of all abstractors and re-abstracting of a random sample (5% of the total from each site) of cases from each site by another team member. Re-abstraction results had 98% agreement with original abstraction results for key analytic items, such as those used to assign screening failure categories.

Automated clinical databases. Health plan enrollment history, dates and departments of all outpatient visits, and mammography history were collected from each health plan's electronic database. Outpatient visits were classified into eight categories: primary care (including internal medicine and family practice), specialty care, vision care, urgent care, physical therapy, obstetrics/gynecology, diagnostic/radiologic testing, and mental health.

The patient's diagnosis date, age at diagnosis, address, race/ethnicity, vital status, tumor size, and stage at diagnosis were obtained from each health plan's cancer registry. Diagnosis dates obtained from the cancer registries were verified by comparing them with dates of histology reports or cytology reports or dates of physician notes in the medical chart. We corrected the date of diagnosis for one patient for whom the cancer registry had made an obvious clerical error (e.g., correct month and day given, but year was 1 year off). We combined race and Hispanic ethnicity data to create a single race/ethnicity variable. Patients were classified as white, non-Hispanic; Hispanic; African American; Asian/Pacific Islander; or other/unknown. Tumor stage was defined by SEER summary stage categories as localized, regional, distant metastases, or unable to determine.

U.S. Census. We used year 2000 U.S. Census–derived variables to characterize each patient's neighborhood as a proxy for individual-level socioeconomic status. We obtained a census block group number for each patient on the basis of her address at the time of diagnosis using a commercial system *(17)* and linked the group numbers to publicly available U.S. Census data [Summary File 3 tables *(18)*]. We considered census block group variables that reflected income, education, and poverty levels. We mapped block group numbers to income, educational, and poverty levels and, on the basis of information in the existing literature *(19)*, defined the following categories of residence: "high-poverty" areas included census blocks with 20% or more persons below the federal poverty level in 1999 and "low-education" areas included census blocks with 25% or more adult women with less than a high school education, as defined by the census variables *(18)*.

Path to diagnosis. We classified patients according to the first event that triggered the cervical cancer diagnostic process by examining the patient's visits and procedures retrospectively from the diagnosis date. The identified trigger event was classified as routine, symptomatic, or fortuitous. Typically, the trigger event was the woman's first abnormal Pap test result. A gap of more than 6 months between screening and/or diagnostic events was considered a break in the diagnostic path. Routine trigger events were those in which patients were diagnosed through routine Pap screening in the absence of cervical cancer symptoms, symptomatic trigger events were those in which patients presented with a complaint of potential cervical cancer symptoms (defined above), and fortuitous trigger events were those in which patients were diagnosed during treatment for a condition unrelated to cervical cancer.

Classification of screening process failures. Patients were classified into the following three categories based on their Pap test histories during the potential intervention period (i.e., the 4- to 36-month period prior to diagnosis): 1) "Failure to Screen" patients had no Pap tests during that period; 2) "Failure in Detection" patients had the initial Pap test result reported as normal, i.e., their first Pap test failed to detect the cervical abnormality that was presumably present; and 3) "Failure in Follow-up" patients had the initial Pap test result reported as abnormal. We defined abnormal cytology on a Pap test as a test result of atypical squamous cells of undetermined significance or more severe. Three patients whose first Pap tests during the potential intervention period were reported as insufficient were classified as Failure in Detection patients. We reclassified eight Failure in Follow-up patients as Failure to Screen patients because the failure-defining abnormal Pap test was performed during months 4–6 prior to diagnosis.

Statistical Analysis

We used SAS statistical software (Version 8.02) for all analyses *(20)*. We used Pearson's chi-square test to test the associations between categorical variables, such as between failure category and demographic, clinical, or tumor-related characteristics. To test associations among the three failure categories and ordered categorical variables, we used the Jonckheere-Terpstra test, a nonparametric test that is designed to test the null hypothesis that the distribution of ordered responses (e.g., age category or SEER summary stage) is the same across the rows of a table (e.g., failure categories). We applied exact methods when the expected cell frequencies were fewer than five.

We used multivariable logistic regression models to identify key differences between cases assigned to each failure category. To define unique characteristics associated with the odds of a woman's diagnosis being ascribed to Failure to Screen, we compared those women with women whose diagnosis was ascribed to failure despite screening (defined as Failure in Detection cases plus Failure in Follow-up cases). We also constructed models that included only women who underwent Pap screening in the potential intervention period to compare the Failure in Detection cases with the Failure in Follow-up cases and examine factors associated with a completed Pap test. All statistical tests were two-sided.

Results

Identification and Characteristics of Patients

We identified 1673 women with invasive cervical cancer diagnosed from January 1, 1995, through December 31, 2000, in the seven participating health plans. Almost half of the women (766 or 46%) were excluded because they had not been a member of the health plan for at least 33 of the 36 months prior to diagnosis. Also excluded were 31 women (2%) with noncervical tumors that had been miscoded as cervical tumors in the registry. Other

women were excluded because of incomplete medical records (13 or 1%) or a lack of definitive evidence that the cancer was invasive (30 or 2%). The remaining 833 women (50%) were included in the study.

Among the 766 women excluded because of insufficient length of health plan membership, 52% were enrolled for less than 1 year; 26% were enrolled for at least 1 year but less than 2 years; and 21% were enrolled for at least 2 years but no more than 33 months. Compared with eligible women, these 766 excluded women were more likely to be younger than 40 years at diagnosis (39% versus 24%, $P<.001$) and to be Hispanic (23% versus 18%, $P = .006$). Excluded women did not differ from eligible women by race or SEER summary stage.

Table 1 shows the demographic and clinical characteristics of the 833 eligible patients. Patients were racially and ethnically diverse; 60% were white, non-Hispanic. The median age at diagnosis was 47 years (range = 16–92 years, interquartile range = 40–59 years). Approximately 17% of the patients were 65 years old or older at diagnosis. The most common tumor types were squamous cell carcinoma (67%) and adenocarcinoma (24%). Many patients (58%) had been health plan members for more than 10 years prior to diagnosis. At 1 year after diagnosis, 88% of the patients were alive, 9% were deceased, and 3% were of unknown vital status. According to census data, 16% of the patients lived in high-poverty areas and 32% lived in low-education areas. Most cancer diagnoses (53%) were triggered by a clinic visit during which the patient reported having a potential symptom of cervical cancer. Only 44% of diagnoses were triggered by a routine screening Pap test in the absence of potential symptoms. The remaining 3% of patients were identified fortuitously during the course of receiving noncervical care. We found a history of cervical neoplasia prior to the potential intervention period in the medical records of 17% of the patients.

Table 1. Demographics of cervical cancer patients

	No. (%)
Total cases	833 (100)
(range: no. cases per health plan)	(22–342)
Age at diagnosis, y	
16–39	201 (24)
40–49	260 (31)
50–64	231 (28)
≥65	141 (17)
Race/ethnicity	
White, non-Hispanic	503 (60)
African American	83 (10)
Asian/Pacific Islander	88 (11)
Hispanic	147 (18)
Other/unknown	12 (1)
Type of cancer	
Squamous cell	555 (67)
Adenocarcinoma	199 (24)
Adenosquamous	42 (5)
Other	37 (4)
SEER summary stage	
Localized	542 (65)
Regional	207 (25)
Distant metastases	54 (7)
Undetermined	30 (4)
Path to diagnosis	
Routine	368 (44)
Symptomatic	441 (53)
Fortuitous	24 (3)

Assignment of Screening Process Failures

As shown in Table 2, for 464 patients (56%), we attributed the diagnosis of cervical cancer to a lack of Pap testing during the potential intervention period (i.e., Failure to Screen). The remaining patients developed invasive cervical cancer despite being screened. We classified 263 patients (32%) as experiencing a Failure in Detection (i.e., the Pap test did not detect a presymptomatic cancer or premalignant abnormality) and 106 patients (13%) as experiencing a Failure in Follow-up (i.e., a premalignant abnormality was detected, but the cancer diagnosis occurred some time later).

Characteristics of Patients According to Screening Failure Category

Table 2 shows the relevant demographic and tumor-related characteristics of patients in each screening failure category. Health plan (data not shown, $P = .035$), path to diagnosis category, reported history of cervical neoplasia (data not shown, $P<.001$), age at diagnosis, type of cancer, SEER summary stage, residence in a high-poverty area, and residence in a low-education area varied statistically significantly among the three failure categories. Only race/ethnicity was not associated with failure category.

We used multivariable logistic regression models to explore whether certain demographic characteristics were independently associated with the odds of a case being ascribed to Failure to Screen (Table 3). Compared with patients who were 16–39 years old at diagnosis, patients who were older at diagnosis had statistically significantly higher odds of having their diagnosis attributed to Failure to Screen (odds ratio [OR] = 6.48; 95% confidence interval [CI] = 3.89 to 10.79). Patients who lived in high-poverty areas (OR = 1.72; 95% CI = 1.11 to 2.67) or in low-education areas (OR = 1.52; 95% CI = 1.07 to 2.16), compared with patients who lived in other areas, had higher odds of having their diagnosis attributed to Failure to Screen. Again, race/ethnicity was not associated with the odds of a diagnosis being assigned as Failure to Screen.

In additional logistic regression models, we compared the cancer diagnoses that occurred among women in the Failure in Detection and Failure in Follow-up categories (i.e., among women whose cancer occurred despite Pap screening) (Table 4). Patients diagnosed with a nonsquamous cell tumor type (primarily adenocarcinomas) were nearly twice as likely as patients diagnosed with a squamous cell tumor type to be assigned to the Failure in Detection category than to the Failure in Follow-up category. Patients whose diagnoses were assigned to the Failure in Follow-up category were nearly twice as likely to live in a low-education area than patients whose diagnoses were assigned to the Failure in Detection category, but that difference was not statistically significant. Patients aged 50–64 years were more than twice as likely as those aged 16–39 years to have their diagnosis assigned to Failure in Follow-up; however, a consistent age trend was not evident.

Characteristics of Patients Whose Diagnoses Were Assigned to Failure to Screen

Given that the majority of the patients (56%) were assigned to the Failure to Screen category, we further examined this group's

Table 2. Association between patient characteristics and screening failure category*

Characteristic	Failure to Screen, % (n = 464)	Failure in Detection, % (n = 263)	Failure in Follow-up, % (n = 106)	P†
Total	56	32	13	
(Health plan range)	(38–60)	(25–47)	(7–18)	.035
Age at diagnosis, y				
16–39	31	51	18	<.001‡
40–49	59	32	9	
50–64	64	21	15	
≥65	72	21	7	
Race/ethnicity				
White, non-Hispanic	57	31	12	.987
African American	57	30	13	
Asian/Pacific Islander	52	35	13	
Hispanic	54	31	15	
Other/unknown	58	33	8	
Type of cancer				
Squamous cell	62	26	12	<.001
Adenocarcinoma	40	46	15	
Adenosquamous	62	26	12	
Other	43	41	16	
SEER summary stage				
Localized	47	37	17	<.001‡
Regional	77	18	5	
Distant metastases	63	32	6	
Undetermined	63	30	7	
Path to diagnosis				
Routine	44	34	22	<.001
Symptomatic	67	28	6	
Fortuitous	33	58	8	
Residence in high-poverty area§‖				
Yes	64	22	14	.037
No	54	34	12	
Residence in low-education area§¶				
Yes	62	24	14	.006
No	53	36	12	

*Some row percentages do not total 100% because of rounding.
†Chi-square test (two-sided) except where noted.
‡Jonckheere-Terpstra test (two-sided).
§Derived from U.S. Census data (n = 792 for census-derived figures due to missing addresses for 41 patients).
‖High-poverty area defined as ≥20% of persons below the federal poverty level.
¶Low-education area defined as ≥25% of adult women with less than a high school education.

Pap screening history before the potential intervention period (i.e., before 36 months prior to diagnosis). No documentation regarding Pap screening during this period was available for 19% of these patients. Many of the remaining patients (49%) had a notation of Pap screening in their medical records less than 10 years prior to the potential intervention period, and 26% had a notation of Pap screening 10 or more years prior to the potential intervention period. Only 7% of these patients had never been screened according to their medical records.

We next examined whether patients assigned to the Failure to Screen category had had any interactions with their health plan during the potential intervention period. During this period, 292 patients (63%) had three or more outpatient visits, 83 patients (18%) had one or two visits, and 89 patients (19%) had no visits.

We further classified patients in this category according to the consistency with which they interacted with their health plan during the potential intervention period. The majority (59%) had consistent interactions (i.e., two or more visits, 6–18 months apart), 22% had sporadic interactions (one or more visits, but not consistent as defined above), and 19% had no interactions. Patients who were at least 50 years old at diagnosis were slightly more likely to have had no interactions with their health plan during this period than patients who were younger than 50 years at diagnosis (21% versus 17%, P = .28). Patients' lack of interaction with their health plans was not associated with race/ethnicity, plan membership duration, or socioeconomic status (data not shown).

Figure 1 shows the percentages of Failure to Screen patients with at least one visit to specific clinic types during the potential intervention period. Of these 464 patients, 329 (71%) had at least one visit to a primary care clinic (i.e., internal medicine, family practice, or general medicine clinic). Among the remaining 135 (29%) patients who did not have a primary care visit, 26 (19%) had at least one visit to a vision care clinic, and 19 (14%) had at least one visit to a specialty care clinic. We reviewed mammography visits for patients who were at least 50 years of age during their potential intervention period (i.e., ages at which yearly mammography screening would be recommended by all participating health plans). Among the 209 Failure to Screen patients who met this criterion, 164 (79%) had not had a mammogram during the potential intervention period.

Characteristics of Patients Whose Diagnoses Were Assigned to Failure in Detection

We further classified the Failure in Detection patients on the basis of their Pap testing history after their first Pap test in the potential intervention period was reported as normal. Of the 263 Failure in Detection patients, 113 (43%) did not have

Table 3. Correlates of Failure to Screen versus Failure Despite Screening*

	No. Failure to Screen patients (n = 440)	No. Failure Despite Screening patients (n = 352)	OR† (95% CI)
Age at diagnosis, y			
16–39	59	131	1.00 (referent)
40–49	145	101	3.18 (2.12 to 4.76)
50–64	138	83	3.84 (2.52 to 5.85)
≥65	98	37	6.48 (3.89 to 10.79)
Race/ethnicity			
White, non-Hispanic	271	208	1.00 (referent)
Asian/Pacific Islander	43	40	0.87 (0.52 to 1.47)
African American	45	35	0.61 (0.35 to 1.04)
Hispanic	74	65	0.83 (0.54 to 1.27)
Other/unknown	7	4	1.44 (0.38 to 5.50)
Residence in high-poverty area‡	81	45	1.72 (1.11 to 2.67)
Residence in low-education area§	158	98	1.52‖ (1.07 to 2.16)

*Failure Despite Screening includes Failure in Detection and Failure in Follow-up. OR = odds ratio; CI = confidence interval.

†Odds ratios reflect the odds of being ascribed as Failure to Screen versus failure despite screening and are adjusted for age at diagnosis, race/ethnicity, health plan, and residence in a high-poverty area (except as noted).

‡High-poverty area defined as ≥20% of persons below the federal poverty level.

§Low-education area defined as ≥25% of adult women with less than high school education.

‖Adjusted for age at diagnosis, race/ethnicity, health plan, and residence in a low-education area.

another Pap test during the potential intervention period and 97 (37%) had no abnormal test results (Pap test or cervical pathology) plus at least one subsequent Pap test reported as normal. The remaining 53 (20%) patients had one or more intervening abnormal tests.

To better understand why the Pap test failed to detect cancer or premalignant cells among patients assigned to the Failure in Detection group, we reviewed the specimen adequacy information on the cytology reports for the 408 Pap tests that were reported as normal. Specimen adequacy information was missing from the cytology reports for 44 (11%) of these tests. Among the remaining 364 Pap tests for which specimen adequacy information was available, 292 (80%) were reported as "satisfactory," 27 (7%) were reported as "satisfactory but limited by no endocervical component," and 45 (12%) were reported as "satisfactory but limited by (other reasons)". None were reported as having unsatisfactory specimen adequacy. Atrophic cells were reported on only eight (2%) of the 408 reportedly normal Pap smears.

Characteristics of Patients Whose Diagnoses Were Assigned to Failure in Follow-Up

We further categorized the 106 Failure in Follow-up patients according to the type and extent of follow-up tests they received, presumably in response to their first abnormal Pap test, during the potential intervention period. Follow-up tests included Pap tests, colposcopy examinations, and cervical biopsies. Only 22 of the 106 patients (21%) did not receive a follow-up test (12 patients had no gynecologic-related visit; 10 patients had a gynecologic-related visit without follow-up testing), whereas 50 patients (47%) received "sporadic" follow-up testing, with more than 6 months between tests. The remaining 34 patients (32%) received "active" follow-up surveillance, with 6 months or fewer between tests. Twenty-one patients (20%) had a notation of patient noncompliance in their medical records. The median time from the date of the failure-defining abnormal Pap test to the date of cancer diagnosis was 22 months (range = 7–54 months).

Table 4. Correlates of Failure in Follow-up versus Failure in Detection*

	No. of Failure in Detection patients (n = 253)	No. of Failure in Follow-up patients (n = 99)	OR (95% CI)
Age at diagnosis, y			
16–39	99	32	1.00 (referent)
40–49	79	22	0.86 (0.45 to 1.65)
50–64	48	35	2.60 (1.37 to 4.91)
≥65	27	10	1.31 (0.53 to 3.20)
Race/ethnicity			
White, non-Hispanic	150	58	1.00 (referent)
Hispanic	44	21	0.80 (0.41 to 1.58)
Other/unknown	59	20	0.54 (0.28 to 1.07)
Nonsquamous cell carcinoma†	104	33	0.55 (0.32 to 0.93)
Residence in high-poverty area‡	28	17	1.98 (0.96 to 4.07)
Residence in low-education area§	62	36	1.77‖ (0.98 to 3.18)

*Odds ratios (ORs) reflect the odds of being ascribed to Failure in Follow-up versus Failure in Detection and are adjusted for age at diagnosis, race/ethnicity, health plan, tumor type, and residence in a high-poverty area (except as noted). CI = confidence interval.

†Histologic tumor types other than squamous cell and adenosquamous carcinoma (primarily adenocarcinoma).

‡High-poverty area defined as ≥20% of persons below the federal poverty level.

§Low-education area defined as ≥25% of adult women with less than high school education.

‖Adjusted for age at diagnosis, race/ethnicity, health plan, tumor type, and residence in a low-education area.

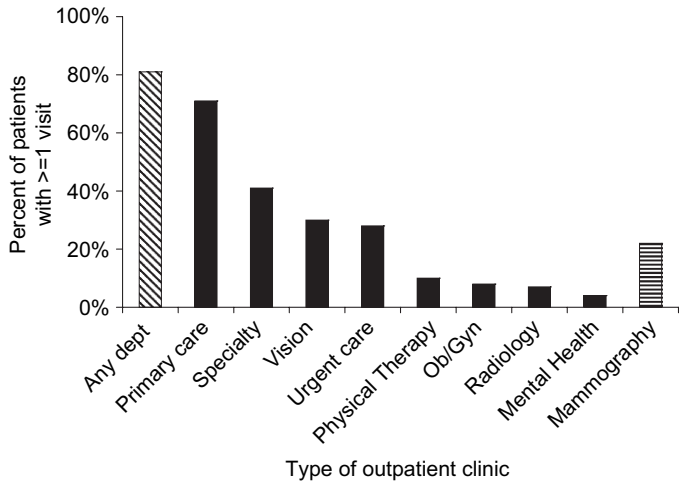

Fig. 1. Specific clinic interactions during the potential intervention period (months 4–36 before diagnosis) among patients whose cancers were ascribed to Failure to Screen. **Diagonal hatched bar** represents the percentage of patients with one or more visit to any outpatient department (excluding mammography). **Solid black bars** represent the percentage of patients with one or more visit to a particular outpatient department. **Horizontal hatched bar** represents the percentage of women with one or more mammography visits among those who were at least 50 years old at the beginning of the period of potential intervention, i.e., women eligible to receive annual mammographic screening under most guidelines.

Discussion

Despite long-term access to Pap smear screening and comprehensive medical care, for the majority of the 833 women with cervical cancer in our study the disease was attributed to a lack of recent Pap screening. This finding is similar to results from other studies of cervical cancer in women with access to health care *(5,11)*, and it suggests that access to care and screening compliance are separable issues in cervical cancer prevention. However, our study differs from those studies in that we included case series from multiple health plan populations, allowing us to investigate a diverse group of cervical cancer patients enrolled in prepaid comprehensive health plans throughout six regions of the United States. In Fig. 2, we summarize our results, propose interventions in response to our findings, and identify subsets of cervical cancer cases that might be alleviated by different categories of intervention.

A limitation of our study is that we excluded nearly 50% of the women who were diagnosed with cervical cancer from 1995 through 2000 at the participating institutions because the woman had been a member of the health plan for less than 3 years prior to diagnosis. Thus, our results provide a description of events preceding cervical cancer only among longer-term members of comprehensive medical care programs. Our results cannot be generalized to populations without comprehensive health care access, nor do they point to possible interventions for earlier detection of cervical cancer among more recently enrolled health plan members. Other limitations of this retrospective study of a case series were that we did not include a noncancer comparison group, nor did we describe Pap test adherence correlates in each health plan membership as a whole. Our goal was to describe attributable factors for screening failures in this group of women who developed cervical cancer. Analogous screening process failures may occur in women who develop neither cervical cancer nor severe precursor lesions.

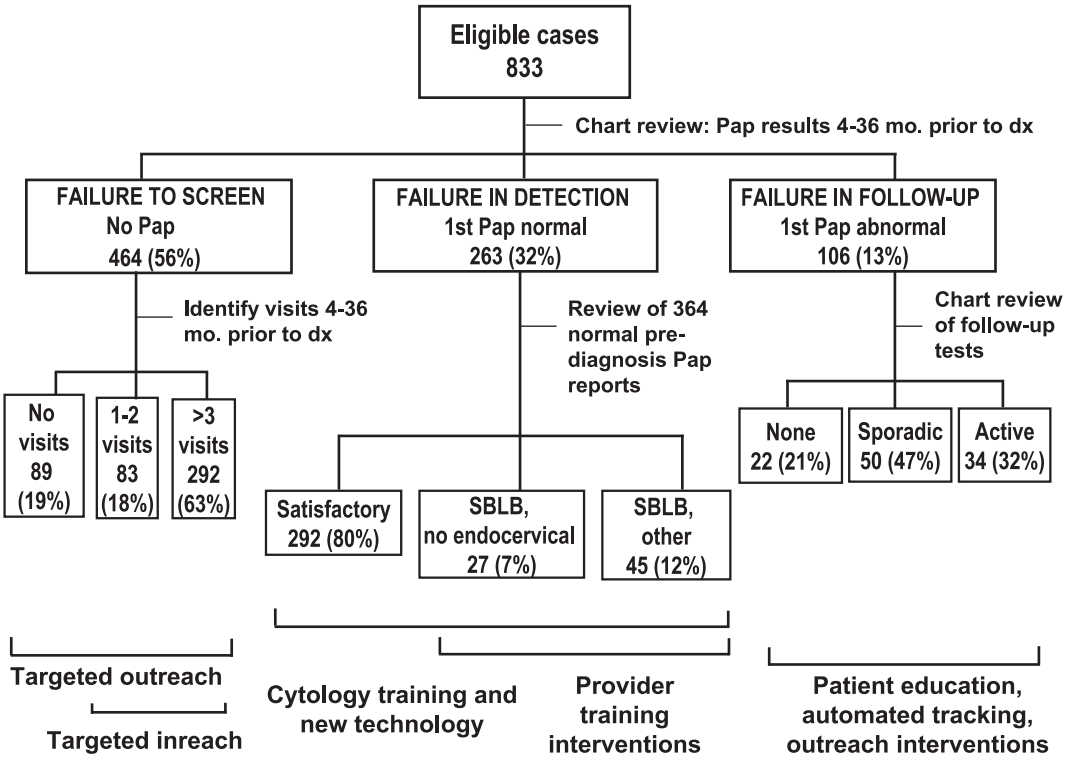

Fig. 2. Classification of cervical cancer cases. Screening process failure categories are subdivided and classified by intervention strategies. The **bottom row** presents potential intervention strategies to decrease the proportion of cervical cancer cases diagrammed above each intervention. SBLB, no endocervical = Pap slides reported as satisfactory, but limited by having no endocervical component present; SBLB, other = Pap slides reported as satisfactory, but limited by factors other than no endocervical component; dx = diagnosis; mo. = month.

A previous study of health plans found that white, non-Hispanic cervical cancer patients were less likely than cervical cancer patients of other races/ethnicities to have their cervical cancer diagnosis attributed to failure to screen *(10)*. By contrast, we found no association between race/ethnicity and any screening failure category. However, we did find that cervical cancer patients who were 65 years or older at diagnosis or who lived in high-poverty or low-education areas were most likely to have their diagnosis be ascribed to a failure to screen.

Almost two-thirds (63%) of the patients whose cervical cancer diagnoses were attributed to failure to screen had at least three outpatient visits (none of which were Pap screening visits) during the potential intervention period. This finding suggests that targeted inreach interventions during nongynecologic visits, particularly those involving primary care, specialty care, or vision care departments, could be an efficient means of promoting adherence to cervical cancer screening (Fig. 2). Although fewer than 22% of patients older than 52 years had had a mammogram during the potential intervention period, those cancer screening visits may also provide opportunities to promote Pap screening. Results of two studies *(21,22)* have suggested that clinician recommendations can be powerful motivators for patient adherence to cancer screening; thus, these nongynecologic visits represent opportunities to facilitate Pap screening. A previous, single-center study reported that nearly 75% of cervical cancer patients who had not undergone Pap screening 3 years prior to diagnosis had had at least one primary care visit during the same period *(23)*. However, that study did not report the comprehensive outpatient clinic visits by department as we did in our study. Our observation that approximately 75% of patients in the Failure to Screen group had a history of Pap testing prior to the potential intervention period suggests that intervention messages that focus on encouraging women to "resume" participation in Pap screening would reach a majority of cervical cancer patients in the Failure to Screen category.

Our finding that almost one-third of the cervical cancer patients had a normal Pap test within the potential intervention period warrants further investigation of these Pap testing failures. Given the slow progression of cervical neoplasia, one would expect at least a precancerous abnormality to be present within 3 years of an invasive cancer diagnosis. The lack of cytologic detection could be attributed to various factors, including suboptimal specimen collection, compromised slide preparation, obscuring factors (i.e., blood or inflammation), or simple misinterpretation. Alternatively, in rare cases of rapid progression, precursor abnormalities may not have been present at the time of initial screening. Improvements in specimen collection in the clinic and in interpretation at the cytology laboratory may help to increase the detection rates (Fig. 2). Of particular interest are the 37% of Failure in Detection patients who had multiple Pap tests, all of which were reported as normal, during the potential intervention period. To further understand the lack of cytologic detection among the Failure in Detection cases, we are pursuing expert review of the 199 available Pap slides that were reported as normal.

Approximately 13% of the cases of cervical cancer were diagnosed in women in whom an abnormality was detected by Pap testing but in whom a definitive diagnosis and treatment were delayed by as much as 54 months (Failure in Follow-up group). Regardless of whether a frank cancer or a precancerous lesion was present at the time of the initial abnormal Pap test results, a more rapid path to diagnosis would be preferred. Among screened women, the older, poorer women were most likely to have had an inefficient follow-up process. To pursue the health care system contribution to follow-up failures, we will investigate whether specific Pap test abnormality categories are more subject to delayed follow-up care and identify the provider characteristics that may influence follow-up care.

Squamous cell carcinomas comprised only 67% of the cervical cancers diagnosed among this population base of highly screened, long-term managed health plan members. By contrast, squamous cell carcinomas comprised 81% of the cervical cancers in a population-based study of cervical cancers in New Mexico (Wheeler C: unpublished observation) and 95% of the cervical cancers in an international collection of cervical cancers, primarily from developing nations *(24)*. These differences may reflect differences in Pap screening intensities among the study populations, as well as the inherent ability of the Pap test to better detect precursors of squamous cell carcinoma (e.g., squamous intraepithelial lesions) than the more endocervically located precursors of adenocarcinoma. Consistent with this explanation, the adenocarcinoma cases in our study were most commonly categorized as Failure in Detection. These results suggest that a substantial proportion of squamous neoplasia in our study population were detected by Pap screening and treated at the precancer stage, leaving fewer cervical neoplasias to present as frank cancer.

Approximately 17% of the cervical cancers in our study were diagnosed among women aged 65 years or older. Given that women older than age 65 have a reduced incidence of cervical cancer *(3)*, several U.S. and international agencies, such as the American Cancer Society and the U.S. Preventive Services Task Force, recommend discontinuation of routine Pap screening at about age 65 if a woman's recent Pap smears were normal and she is not at high risk of the disease *(25)*. Thus, efforts to increase cervical cancer screening among women older than 65 years must be balanced with the recognition that only a small proportion of these women may benefit from such intervention.

To ensure early detection of this preventable cancer, health plans should improve Pap screening compliance, particularly among the older and poorer members who are at high risk of developing cervical cancer. Adjunctive testing for persistent infection with human papillomavirus (HPV), which is the cause of virtually all cervical cancers, may identify women who are at the highest risk of developing cervical cancer *(26)*. Such testing might distinguish the few older women who have persistent HPV infections and thus the highest risk of developing cervical neoplasia, from the majority of women, who have no detectable HPV infection and a very low risk of developing cervical cancer. Such an approach may help focus screening efforts on older women who are truly at risk and direct lower-risk women to lesser monitoring.

Despite the many exciting new technologies that may improve our ability to predict or detect cervical neoplasia, we must not lose sight of the need to increase screening adherence. Even the most perfect screening method will not detect disease in a woman who has not participated in the prevention process.

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Notes

W. Leyden and M. Manos hold stock in Digene (the makers of an HPV test). M. Manos holds stock in Cytyc (the makers of a liquid-based cytology system for cervical cancer screening).

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