Cervical cancer is the second most commonly diagnosed cancer in women worldwide; in 2002, half a million incident cases of cervical cancer were reported and there were more than a quarter of a million deaths from this disease (1). In many industrialized countries, the incidence of cervical cancer has decreased by the use of Pap smear screening. In Sweden, for example, the overall incidence of cervical cancer declined by 67% over a 40-year period, from 20 cases per 100,000 women (world standard rate) in 1965 to 6.6 cases per 100,000 women in 2005 (2).

The major cause of cervical cancer is infection with oncogenic types of human papillomavirus (HPV) (3). Although vaccines to prevent infection with specific oncogenic HPV types are now available, it will take many years for their effects on cervical cancer morbidity to be known (4). Until then, cervical cancer screening programs will remain the primary preventive strategy for this cancer (5).

The rationale for cervical cancer prevention by screening is primarily to reduce the incidence of the disease through the detection and removal of precancerous lesions and secondarily to reduce disease progression through the detection of invasive cancers in the early stages, thereby improving chances for a cure and reducing mortality. Cytological screening for cervical cancer (ie, via a Pap smear) is highly effective in reducing the incidence of squamous cell cervical cancer (6).

**Background**

The effectiveness of cervical cancer screening programs differs widely in different populations. The reasons for these differences are unclear. Routine and comprehensive audits have been proposed as an ethically required component of screening. We performed a nationwide audit of the effectiveness of the Swedish cervical cancer screening program.

**Methods**

We identified all invasive cervical cancer cases that were diagnosed in Sweden from January 1, 1999, through December 31, 2001, and had been reported to the Swedish Cancer Registry (n = 1230 cases). We verified the diagnoses by histopathologic rereview and matched each case subject to five (population-based) age-matched control subjects who were identified from the National Population Register. The Pap smear screening histories for case and control subjects were reviewed for a 6-year period using the National Cervical Cancer Screening Register, which contains data on essentially all relevant cytological and histological diagnoses in Sweden. Odds ratios (ORs), and their 95% confidence intervals (CIs), of cervical cancer according to screening history were calculated in conditional logistic regression models. All statistical tests were two-sided.

**Results**

Women who had not had a Pap smear within the recommended screening interval had higher risk of cervical cancer than women who had been screened (OR = 2.52, 95% CI = 2.19 to 2.91). This risk was similarly increased for all age groups ($P_{\text{homogeneity}} = .96$). The risk for nonsquamous cell cervical cancers (OR = 1.59, 95% CI = 1.20 to 2.11) was also increased. Women who had not had a Pap smear within the recommended screening interval had a particularly high risk of advanced cancers (OR = 4.82, 95% CI = 3.81 to 6.44). Among women who had been screened within the recommended interval, those with abnormal Pap smears had a higher risk of cervical cancer than those with normal smears (OR = 7.55, 95% CI = 5.88 to 9.69) and constituted 11.5% of all women with cervical cancer.

**Conclusions**

Nonadherence to screening intervals was the major reason for cervical cancer morbidity. The screening program was equally effective for women of all ages and was also effective against nonsquamous cancers.
Subjects and Methods

The Swedish Cervical Cancer Screening Program

Organized screening for cervical cancer was introduced in Sweden between 1967 and 1977 (17). The national guidelines for organized cervical screening recommend Pap smear screening for all women between the age of 23 and 60 years, with 3-year screening intervals for women aged 23–50 years and 5-year intervals for women aged 51–60 years (18). Women older than 60 years are not invited to the cervical cancer screening program in Sweden because women who have been screened up to age 60 and have had no previous abnormal smears are considered to be at low risk for cervical cancer. Because health care in Sweden is organized at the county level, there are minor differences in how these national recommendations are implemented, particularly in terms of age limits and screening intervals (18). For example, in 5 of 21 counties, women who are eligible for invitation to the screening program are identified by birth cohort, whereas in the other 16 counties, eligible women are identified by the time that has elapsed since their last Pap smear. Information on all Pap smears taken within or outside the organized screening program in a county is stored in a common database; therefore, women who have Pap smears taken outside the organized program are invited for screening but not until a time period equal to a screening interval has elapsed.

Identification of Case and Control Subjects

All cases of invasive cervical epithelial carcinoma and unspecified uterine cancer (19) that were reported to the nationwide Swedish Cancer Registry for the 3-year period from January 1, 1999, through December 31, 2001, were retrieved. Swedish physicians and pathologists are required to report all new cancers to this registry (2,20). To verify that all cervical cancer cases included in the cancer register were actually cervical cancers, we obtained the archival histological specimens of all registered cervical cancers and subjected them to histopathologic re-review by an expert pathologist (WR). No archival histological specimens were available for 40 cases. However, we included these 40 cases in the analysis because the clinical and pathology records for these cases indicated that they had been reviewed and that the reviews had verified the original diagnosis of primary invasive cervical carcinoma.

A total of 1335 cervical cancer cases were reported to the Cancer Registry from January 1, 1999, through December 31, 2001. Upon histopathologic re-review, we excluded 45 cases of cancers of non-cervical origin, 1 case of nonepithelial cervical cancer, 47 cases of noninvasive cancers, and 23 cases that were recurrences of cervical cancer according to the cancer registry. Among the 89 unspecified uterine cancers that were reported to the Cancer Registry during this time period, 11 were found to be cervical cancers upon histopathologic re-review and were included in the analysis. Altogether, 1230 case subjects were included. Of 6150 age-matched control subjects, 26 were excluded because they had been previously diagnosed with cervical cancer; thus, 6124 control subjects were included.

All case subjects were classified by their age at diagnosis and by clinical tumor stage (microinvasive [stage IA], localized [stage IB], or advanced [stage II or higher]) according to International Federation of Gynecology and Obstetrics (FIGO) guidelines (21) (Table 1). Information about the tumor stage at diagnosis for each case subject was collected from regional databases or from clinical records that were kept by the clinical departments that reported the cases to the cancer registry. All case subjects were also classified by histological type (squamous cell carcinoma, adenocarcinoma, adenosquamous carcinoma, or “other epithelial tumor,” which included neuroendocrine, poorly differentiated, and small cell cancer, although its effect on the incidence of adenocarcinoma is less well established (6,7). However, the effect of screening programs on cervical cancer morbidity at the population level has varied substantially among different countries, primarily because of differences in the implementation of organized screening and coverage of the target population (8–12). Cervical cancer still occurs even in countries that have an organized program for cytological screening of cervical cancer, but the reasons need to be clarified in more detail to enable targeted improvement. Although the need for routine and comprehensive audits of screening programs that include the entire population that is being targeted by a program has been emphasized repeatedly (13–15), such audits have so far not been implemented. Audits may greatly assist in improving the effectiveness of screening programs that are intended to prevent cancer by evaluating the extent of the morbidity that can be affected by changes in program organization, screening methods, or treatment and follow-up strategies for treating abnormalities detected by screening (8,11,16).

We developed a protocol for a comprehensive nationwide audit of the Swedish cervical cancer screening program. The aims of the audit were to set the standards for routine monitoring of the reasons why cervical cancers still occur despite organized screening and to assist in prioritizing efforts to improve the effectiveness of screening programs.

CONTEXT AND CAVEATS

Prior knowledge

The effectiveness of cervical cancer screening programs differs widely in different populations, but the reasons are unclear. Routine and comprehensive audits have been proposed as an ethically required component of screening.

Study design

A comprehensive nationwide audit of the effectiveness of the organized cervical cancer screening program in Sweden.

Contribution

Not having had a Pap smear taken within the recommended screening interval was the most important risk factor for cervical cancer in the presence of a screening program. The screening program was equally effective for women of all ages, including women younger than 30, and was also effective against nonsquamous cancers.

Implications

Compliance with screening recommendations and high population coverage of screening are vital for success.

Limitations

Attendance to the screening program (ie, the relationship between invitations issued and tests performed) was not studied because only some counties kept identifiable information on when and to whom invitations had been issued.
1995 or later are nearly 98% complete; the missing data are from a use in Sweden (22). Cytology data for women who were tested in diagnostic codes. All diagnostic codes for cytology and all combinations that identifies the laboratory that analyzed the test, and one or more diagnostic codes. Each report notes the personal identification number of the woman for whom the benefit of screening has been questioned; those aged 30–65, for whom Pap smears should be taken within the recommended screening interval; and those older than 65, who are expected to be at low risk of cervical cancer provided that they have had only normal Pap smears up to the age of 60 (Table 1).

Each case subject was matched by year of birth to five control subjects who were randomly selected from the National Population Register at Statistics Sweden (Örebro, Sweden). Each control subject had to be alive on the date of diagnosis for the case subject and not have been diagnosed with cervical cancer up to the date of diagnosis for the respective case subject. All residents of Sweden are assigned a unique personal identification number that allows the linkage of data, for example, between health care registers and population registers. We used these numbers to identify all case and control subjects and to link them to all registers and clinical records. This study was approved by the Ethical Review Boards in Uppsala, Stockholm, Umeå, Gothenburg, and Lund and the joint board of Örebro and Linköping, Sweden.

**Screening History**

The National Cervical Cancer Screening Register (Stockholm, Sweden) collects all cervical cytology and histopathology reports for women who underwent cervical cancer screening in Sweden beginning in 1993; these reports are provided by the diagnostic databases at all 30 pathology and cytology laboratories in Sweden. Each report notes the personal identification number of the woman who was tested, the date of the test, the specimen number, a code that identifies the laboratory that analyzed the test, and one or more diagnostic codes. All diagnostic codes for cytology and all combinations of codes used in these reports were converted to the 14 Systematized Nomenclature of Medicine codes that are currently in use in Sweden (22). Cytology data for women who were tested in 1995 or later are nearly 98% complete; the missing data are from a single laboratory that provides services to 1.3% of the population of Sweden. Cytology data for women who tested in 1993 and 1994 are 93% and 97% complete, respectively.

An evaluable screening history was defined as the availability of all smears and cervical histopathology specimens during the 6-year period that started 6.5 years before and ended 6 months before the date of cervical cancer diagnosis for case subjects or the corresponding date for the control subjects. We chose this period because 1) 6 years corresponds to two screening rounds in the 23- to 50-year age group and 2) 6.5 years was the longest time for which we had access to nationwide data for all case and control subjects in this study. In addition, the process of evaluation and treatment of an abnormal smear normally takes up to half a year. Pap smears or biopsies that were taken during the 6 months before the date of cancer diagnosis were therefore not considered as part of the evaluable screening history for case or control subjects but rather as tests that led to the detection of invasive cancer (16).

To avoid differential exclusion of screening tests for case subjects, we assessed the screening histories of all subjects during a window of screening exposure that was exactly one screening interval long (as defined by the subject’s age) and that ended 6 months before the cervical cancer diagnosis (23,24). A woman was considered to have been tested within the recommended screening interval if she was 53 years or younger and had a smear taken from 6 to 42 months (0.5–3.5 years) before a cervical cancer diagnosis; for women aged 54–65 years, for whom a 5-year screening interval applies, the smear had to be taken from 6 to 66 months (0.5–5.5 years) before the cervical cancer diagnosis. We also assessed whether women aged 66 years or older had had a smear taken within 0.5–6.5 years before a cancer diagnosis. Screening was defined as normal if at least one smear had been taken within the recommended interval of the screening program and no cytological abnormality was reported in the period 0.5–6.5 years, that is, more than one screening interval, before the cancer diagnosis of the case subject. A screened woman was considered to have had an abnormal smear if a test was taken within the recommended interval and at least one smear had atypical squamous cells of uncertain significance, a low-grade squamous intraepithelial lesion, or a high-grade squamous intraepithelial lesion in the period 0.5–6.5 years before cancer diagnosis. A smear that was labeled “not satisfactory for evaluation” was also classified as abnormal unless it was followed by a normal smear. An abnormal smear that was followed by a report of a histopathologic specimen was considered to indicate an assessment with a biopsy by a gynecologist. Pap smears that were taken during the 6 months before a cervical cancer diagnosis were analyzed separately to see if there was a shift toward lower FIGO stages among case subjects whose cancers were presumed to be screen detected. For this analysis, symptomatic cases were defined as those for which a Pap smear was taken less than 1 month before diagnosis or for which no Pap smear was taken during the 6 months before diagnosis and screen-detected cases were defined as those for which a Pap smear was taken 1–6 months before diagnosis.

**Statistical Methods**

The Pearson χ² test was used to test for independency in FIGO stage distribution between case subjects with and without a Pap smear within the recommended screening interval, between case
Results

A total of 1230 case subjects—all of whom were classified by age at diagnosis, FIGO stage, and histopathologic type—were included in this study (Table 1). Approximately two-thirds of the case subjects (n = 840) were younger than 66 years at diagnosis and thus had fully evaluable screening histories. The distribution of case subjects by age at diagnosis and FIGO stage is presented in Figure 1.

Sixty-three (5%) of the 1230 case subjects were younger than age 30 years at diagnosis (Table 1); only one case subject was younger than 23 years at diagnosis (data not shown). Squamous cell carcinoma was the predominant histological type in all age groups, and adenocarcinomas were more common among women who were 30–65 years old at diagnosis than among women who were younger than 30 or older than 65 at diagnosis (Table 1).

Of the 39 women who were diagnosed with a small cell, poorly differentiated, or neuroendocrine cervical carcinoma, 29 did not have a Pap smear taken during the recommended screening interval and 28 had advanced-stage disease (data not shown). Twenty-six of these 39 women were older than 60 at diagnosis (data not shown).

A total of 789 (64%) of all case subjects and 394 (83%) of the 477 case subjects who were diagnosed with advanced cervical cancer (FIGO stage II or higher) did not have a Pap smear taken during the recommended screening interval (Table 2). Approximately 50% of the case subjects who did not have a Pap smear during the recommended screening interval were diagnosed with advanced disease, compared with less than 19% of those who did have a Pap smear during the recommended interval (P_{\text{FIGO stage}} < .001) (Table 2). The proportion of cancers at higher FIGO stages increased steadily with increasing age at diagnosis (Figure 1), and 55% of the advanced-stage cancers (264/477) were diagnosed in women who were older than 65 and did not have a Pap smear within 0.5–6.5 years before diagnosis (data not shown).

Women who had not had a Pap smear taken within the recommended screening interval had a higher risk of cervical cancer than women who had been tested (OR = 2.52, 95% CI = 2.19 to 2.91) (Table 3). Risks of both squamous cell carcinoma (OR = 2.97, 95% CI = 2.51 to 3.50) and nonsquamous (primarily adenocarcinoma) cervical carcinoma (OR = 1.59, 95% CI = 1.20 to 2.11) were increased.

Among screened women, those whose Pap smears were abnormal had a higher risk of cervical cancer than those whose smears were normal (OR = 7.55, 95% CI = 5.88 to 9.69) (Table 3). Of the 1230 case subjects, 141 (11.5%) had an abnormal Pap smear. Of the 6124 control subjects, 191 (3.1%) had an abnormal Pap smear. However, only 4.2% (20/477) of the case subjects with advanced cancer had an abnormal Pap smear. Among women who had an abnormal Pap smear, those who did not have a follow-up biopsy had a higher risk of cervical cancer than those who did (OR = 1.89, 95% CI = 1.19 to 3.02). The risk of any cervical cancer for women without a Pap smear vs women with a Pap smear was statistically significantly increased with increasing FIGO stage (OR_{\text{microinvasive cancer}} = 1.70, 95% CI = 1.28 to 2.26; OR_{\text{localized cancer}} = 2.10, 95% CI = 1.71 to 2.59; OR_{\text{advanced cancer}} = 4.82, 95% CI = 3.61 to 6.44; \( P_{\text{homogeneity}} < .001 \) (Table 3). We observed a similar pattern of increasing risk with increasing FIGO stage for nonsquamous cervical carcinomas, but it was not statistically significant (\( P_{\text{homogeneity}} = .29 \)). The risk of cervical cancer for women without vs with a Pap smear was similarly increased for all age groups (\( P_{\text{homogeneity}} = .96 \); Table 3).

**Table 1.** Histological type according to age at diagnosis and FIGO stage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Squamous cell carcinoma, n (%)</th>
<th>Adenocarcinoma, n (%)</th>
<th>Adenosquamous cell carcinoma, n (%)</th>
<th>Small cell, poorly differentiated, or neuroendocrine carcinoma, n (%)</th>
<th>All types, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases</td>
<td>921 (74.9)</td>
<td>243 (19.8)</td>
<td>27 (2.2)</td>
<td>39 (3.2)</td>
<td>1230 (100)</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21–29</td>
<td>52 (82.5)</td>
<td>9 (14.3)</td>
<td>0 (0)</td>
<td>2 (3.2)</td>
<td>63 (100)</td>
</tr>
<tr>
<td>30–65</td>
<td>563 (72.5)</td>
<td>177 (22.8)</td>
<td>21 (2.7)</td>
<td>16 (2.1)</td>
<td>777 (100)</td>
</tr>
<tr>
<td>≥66</td>
<td>306 (78.5)</td>
<td>57 (14.6)</td>
<td>6 (1.5)</td>
<td>21 (5.4)</td>
<td>390 (100)</td>
</tr>
<tr>
<td>FIGO stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>208 (82.9)</td>
<td>40 (15.9)</td>
<td>3 (1.2)</td>
<td>0 (0)</td>
<td>251 (100)</td>
</tr>
<tr>
<td>IB</td>
<td>336 (66.9)</td>
<td>140 (27.9)</td>
<td>15 (3.0)</td>
<td>11 (2.2)</td>
<td>502 (100)</td>
</tr>
<tr>
<td>II or higher</td>
<td>377 (79.0)</td>
<td>63 (13.2)</td>
<td>9 (1.9)</td>
<td>28 (5.9)</td>
<td>477 (100)</td>
</tr>
</tbody>
</table>

* FIGO = International Federation of Gynecology and Obstetrics; IA = microinvasive cancer; IB = localized cancer; II or higher = advanced cancer.
The FIGO stage distribution for all case subjects (n = 1230) was 20.4% stage IA disease, 40.8% stage IB, and 38.8% stage II or higher. For the presumably screen-detected cases (ie, those with a Pap smear taken 1–6 months before diagnosis; n = 305), the stage distribution was further shifted toward earlier stages; 46.5% had stage IA, 45.6% had stage IB, and 8.9% had stage II or higher compared with symptomatic cases (P<.001; Table 2). We detected no increase in screening intensity among either the case subjects or the matched control subjects during the year before the window of screening exposure (data not shown).

**Discussion**

Here, we report results of a comprehensive nationwide audit of an organized cervical cancer screening program. The key features of the audit were 1) use of nationwide cancer registry to identify cervical cancer cases; 2) histopathologic review of diagnostic slides; 3) inclusion of unspecified uterine cancers in the review, which identified additional verified cervical cancers; 4) nationwide and comprehensive collection of all cytological and histopathologic data, including smears taken outside the organized screening program; 5) control subjects who were identified from the nationwide population register; and 6) permission from ethical review boards to evaluate the effect of the program on the entire population without having to obtain informed consent, using data on individual subjects from national registers. Because we used the same source of screening history data for the case and control subjects and a window of exposure to screening that was equal to one screening interval, we were able to avoid selection, recall, and testing biases (23–25). As expected, we found that not having had a Pap smear taken within the recommended screening interval was the most important risk factor for cervical cancer in the presence of a screening program: approximately 64% of all cervical cancers and 83% of the advanced cases were diagnosed in women who were not tested. Screening was also associated with decreased risks of cervical cancer among women who were younger than 30 or who were older than 65 years. Together, these results indicate that compliance with screening recommendations and high population coverage of screening are vital for success and that attention should be paid to underscreened older women.

Only a few attempts have been made to comprehensively audit an organized screening program (11,26). The largest audit published to date is from the United Kingdom (16). In that study, the odds ratios of acquiring invasive cervical cancer of stage IB or higher after 3 years since the last negative smear were 0.28 and 0.12 at ages 20–39 and 40–54, respectively, compared with women with no previous negative smear. After 5 years, the corresponding odds ratios were 1.03 and 0.39, respectively. Although the UK audit used a different approach to estimate the relative protection of cervical cancer screening (time since last negative smear) and only included invasive cervical cancers of stage IB or higher, their results are in accordance with what we found, with one exception. The UK audit concluded that screening afforded less protection against cervical cancer among younger women, whereas we found no evidence that younger women without a Pap smear within the recommended screening interval should be at a relatively lower risk than older women. The reason for this discrepancy could be the different methodological approaches used, but it is also possible that there are real differences in the natural history of the disease or in the effectiveness of cervical cancer screening programs among countries.

Epidemiological evaluation of the effectiveness of screening commonly relies on the identification of trends in incidence or
mortality rates over time. However, because the background risks may also change over time, this approach can be problematic, particularly when analyzing subgroups that have small numbers of cases because they tend to have limited statistical power in analyses that evaluate short time spans. Two such subgroups that have been difficult to study with respect to the effect of screening are women younger than 30 and women diagnosed with adenocarcinoma (26,27). In both of these groups, the incidence of cervical cancer has not declined since screening was introduced, and in some countries incidence has even increased (6,9,26–30). Our access to complete databases, combined with the fact that both the case and control subjects were identified from the nationwide population register, made it possible to study the effectiveness of the Swedish cervical cancer screening program in these subgroups in a reliable manner and with adequate statistical power. There was clear evidence that the screening program was effective in reducing the incidence of cervical cancer in women younger than 30 and also that it reduced the incidence of adenocarcinoma (Table 3). One interpretation of the stable, or even increasing, incidences of cervical cancer in women younger than 30 years of age and of adenocarcinoma of the cervix is that they are the net result of increases in background risks and the counteracting effect of the screening program (31–33).

Table 3. ORs of cervical cancer associated with screening history, age at diagnosis, and FIGO stage by histological type*

<table>
<thead>
<tr>
<th>Variable</th>
<th>All cancers</th>
<th>Squamous cell carcinomas</th>
<th>Nonsquamous cell carcinomas†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of case subjects</td>
<td>No. of control subjects</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>All subjects</td>
<td>1230</td>
<td>6124</td>
<td></td>
</tr>
<tr>
<td>Screening history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not screened</td>
<td>789</td>
<td>2836</td>
<td>2.52 (2.19 to 2.91)</td>
</tr>
<tr>
<td>Screened‡</td>
<td>441</td>
<td>3288</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Not screened</td>
<td>789</td>
<td>2836</td>
<td>3.53 (3.02 to 4.13)</td>
</tr>
<tr>
<td>Screened, Pap smear normal</td>
<td>300</td>
<td>3097</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Screened, Pap smear abnormal</td>
<td>141</td>
<td>191</td>
<td>7.55% (5.88 to 9.69)</td>
</tr>
<tr>
<td>Screened, Pap smear normal</td>
<td>300</td>
<td>3097</td>
<td>1.00 (referent)</td>
</tr>
<tr>
<td>Abnormal Pap smear, no biopsy</td>
<td>91</td>
<td>93</td>
<td>1.89% (1.19 to 3.02)</td>
</tr>
<tr>
<td>Abnormal Pap smear with biopsy</td>
<td>50</td>
<td>98</td>
<td>1.00 (referent)</td>
</tr>
</tbody>
</table>

Age at diagnosis, y

21–29

Not screened | 37 | 120 | 2.37 (1.36 to 4.13) | 32 | 100 | 2.61 (1.40 to 4.85) | 5 | 20 | 1.69 (0.45 to 6.33) |
| Screened    | 26 | 189 | 1.00 (referent)    | 20 | 153 | 1.00 (referent)    | 6 | 36 | 1.00 (referent)    |

30–65

Not screened | 394 | 1142 | 2.51 (2.14 to 2.94) | 311 | 847 | 2.93 (2.43 to 3.53) | 83 | 295 | 1.65 (1.21 to 2.26) |
| Screened    | 383 | 2733 | 1.00 (referent)    | 252 | 1969 | 1.00 (referent)    | 131 | 764 | 1.00 (referent)    |

≥66

Not screened | 358 | 1574 | 2.79 (1.89 to 4.11) | 285 | 1220 | 3.59 (2.25 to 5.74) | 73 | 354 | 1.26 (0.61 to 2.59) |
| Screened    | 32  | 366  | 1.00 (referent)    | 21  | 299  | 1.00 (referent)    | 11  | 67  | 1.00 (referent)    |

FIGO stage

IA

Not screened | 122 | 450 | 1.70 (1.28 to 2.26) | 107 | 383 | 1.83 (1.34 to 2.49) | 15 | 67 | 1.10 (0.53 to 2.27) |
| Screened    | 129 | 799 | 1.00 (referent)    | 101 | 653 | 1.00 (referent)    | 28 | 146 | 1.00 (referent)    |

IB

Not screened | 273 | 968 | 2.10 (1.71 to 2.59) | 201 | 670 | 2.55 (1.97 to 3.29) | 72 | 298 | 1.46 (1.01 to 2.11) |
| Screened    | 229 | 1534 | 1.00 (referent)    | 135 | 1004 | 1.00 (referent)    | 94 | 530 | 1.00 (referent)    |

II or higher

Not screened | 394 | 1418 | 4.82 (3.61 to 6.44) | 320 | 1114 | 5.79 (4.14 to 8.08) | 74 | 304 | 2.40 (1.27 to 4.52) |
| Screened    | 83  | 955  | 1.00 (referent)    | 57  | 764  | 1.00 (referent)    | 26  | 191 | 1.00 (referent)    |

* Odds ratios and 95% confidence intervals were calculated with conditional logistic regression except where noted. OR = odds ratio; CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; IA = microinvasive cancer; IB = localized cancer; II or higher = advanced cancer.
† Includes adenocarcinoma, adenosquamous cell carcinoma, and poorly differentiated, small cell, and neuroendocrine carcinoma.
‡ A Pap smear was taken during the last screening interval.
§ Odds ratios and 95% confidence intervals were calculated using unconditional logistic regression, controlling for age at diagnosis.
|| Test for homogeneity over age-at-diagnosis groups.
¶ Test for homogeneity over FIGO stage groups.
Screening of women younger than 30 years of age has been described as having little benefit because of the faster progression from precursors to cancer and a higher proportion of non-squamous cell cancers compared with older age groups (16,27,34). In this audit, the lowest proportion of non-squamous cell cervical cancer cases was in the under-30 age group. Although our data support screening of women who are younger than 30 years of age, the fact that only one case of invasive cervical cancer occurred in a woman who was younger than the lower age limit of the screening program supports the view that screening of women younger than 23 is unnecessary.

We found that women older than 65 who had a Pap smear taken during the previous 6.5 years had a statistically significant lower risk of cervical cancer compared with those who did not have a Pap smear taken during that time (Table 3). However, women older than 65 with a Pap smear in the last 6.5 years may also have participated to a greater extent in screening before the age of 60 than women of the same age who did not have a recent Pap smear. Because we did not have data to study this hypothesis, the finding should not be taken as evidence that screening should be extended after the age of 60 in women who have previously had normal Pap smears. Our finding that screening is associated with reduced risks for advanced-stage cervical cancers is in accordance with results of previous studies (9,35,36).

The strongly elevated risk of cervical cancer (OR = 7.55, 95% CI = 5.88 to 9.69) associated with having an abnormal smear can be seen as a failure in the screening system (Table 3). Unless an abnormal smear signals an already invasive cancer, having an abnormal Pap smear per se should not necessarily be associated with an increased risk of cervical cancer because the subsequent assessment and possible treatment should protect a woman from invasive cancer; indeed this is the very foundation of screening. The finding that 11.5% of the cervical cancer case subjects in our study had an abnormal Pap smear as opposed to only 3.1% of control subjects implies that the risk of cervical cancer could also be reduced by improving the management of abnormal Pap smears. Furthermore, women with abnormal Pap smears who did not have a follow-up biopsy had a higher risk of cervical cancer than those with a follow-up biopsy (OR = 1.89, 95% CI = 1.19 to 3.02). There are several reasons why an abnormal smear may not be followed by a biopsy: 1) the smear may be overlooked or ignored by the medical professionals; 2) the woman may refrain from follow-up; 3) the follow-up may have been only a repeated Pap smear, which has been an accepted and common procedure in Sweden for low-grade and borderline abnormalities; and/or 4) a follow-up examination with colposcopy may not have found any lesion on which to perform a biopsy. This study cannot differentiate between these possibilities. However, the fact that 7% of the cancer cases in our study were diagnosed in women who had an abnormal smear that was not followed up with histopathology indicates that the assessment of abnormal smears is an area that needs improvement, as has been pointed out in several studies (10,11,37,38).

The main focus of our audit was to evaluate the effectiveness of an organized screening program in preventing invasive cervical cancer through the detection and further assessment of precursors, procedures that can take up to 6 months. Therefore, we omitted from the analysis any smears that were taken within 6 months of a diagnosis from both the case subjects and the matched control subjects. This approach does not exclude smears that potentially could have prevented disease that had already advanced to the occult invasive phase (24). For all case and control subjects, we used the same “window of exposure” to screening, which corresponded to exactly one age-related screening interval that ended 6 months before the case subject’s diagnosis, so we can conclude that there was no differential exclusion of screening tests for the case subjects (23,24).

Smears taken within 6 months of diagnosis of the cancer could not have prevented the invasive cancer because it was already there before the assessment and treatment process was finished. These smears are, however, interesting in another respect. Screen detection of invasive cancer may be beneficial to the prognosis of a cancer patient due to detection at earlier stages. Such a benefit seems to be present given that the stage distribution among presumably screening-detected invasive cancers in our study was shifted toward lower stages.

A weakness of this audit was that we were not able to study attendance to the screening program—that is, the relationship between invitations issued and tests performed—because only some counties kept identifiable information on when and to whom invitations had been issued. Future audits should examine whether a lack of screening is due to the failure to issue invitations or to nonresponse to a screening invitation. Quality assurance of the “fail-safe” systems in use is important to ensure that all eligible women are indeed invited and that the screening tests are taken without delay (13,39–41).

In summary, this study highlights the benefit of reliable population-based registers in the analysis of reasons for remaining incidence of cervical cancer in spite of existence of an organized screening program. As expected, imperfect population coverage of screening was by far the most important risk factor for incident cervical cancer. Abnormal smears, particularly if not followed up by a biopsy, were also an important risk factor, which suggests that improved follow-up programs are warranted. On the other hand, it was possible to demonstrate a beneficial effect of screening in younger women and against adenocarcinomas of the cervix.

References


**Funding**

The Swedish Cancer Society (02–6988); Research and Development Center of Gävleborg County (2002–03–27).

**Notes**

The National Cervical Cancer Screening Registry was supported by the Swedish National Board of Health and Welfare.

The funding bodies had no role in data extraction and analyses, in the writing of the manuscript, or in the decision to submit the manuscript for publication. Manuscript received August 20, 2007; revised February 15, 2008; accepted March 4, 2008.