Endocervical Status Is Not Predictive of the Incidence of Cervical Cancer in the Years After Negative Smears

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Abstract

The clinical relevance of the lack of endocervical cells was never well established in a longitudinal study with histologically proven cervical cancer as an end point. From the Dutch Network and National Database for Pathology, results for all negative smears obtained in 1990 and 1991 in the Netherlands were retrieved, as were data for all cytologic and histologic examinations performed after the negative smears before April 1998. There were no significant differences between the proportion of preinvasive lesions (cervical intraepithelial neoplasia 1, 2, and 3) detected after negative smears without endocervical cells compared with negative smears with endocervical cells. The proportion of women in whom invasive cancer developed was the same in both groups. These data suggest there is no reason to advise women with negative smears without endocervical cells to undergo an additional smear.

In the literature, there is no agreement about the clinical relevance of negative Papanicolaou smears without endocervical cells. The presence of endocervical cells usually is considered an indicator of an adequate sample. This view is supported by cross-sectional studies, in which a lower proportion of abnormalities has been reported in smears without endocervical cells compared with smears with endocervical cells,1-3 and by retrospective studies, in which rescreened negative smears before the diagnosis of cervical intraepithelial neoplasia (CIN) 3 or invasive cancer showed a high proportion of negative smears without endocervical cells.4-6 These results suggest that smears without endocervical cells are associated with a higher false-negative rate. However, longitudinal studies showed no increase of detected abnormalities after a smear without endocervical cells compared with negative smears with endocervical cells,7,8 although these studies are based on small numbers of smears, short follow-up times, and cytologically detected CIN as the end point.

Until 1996 in the Netherlands,9 all women with negative smears without endocervical cells were recommended to have an additional smear after 1 year; thereafter, they returned to the regular program of smears with a 3-year interval. In 1996, the guidelines were changed to recommend an additional smear after 6 months and a screening interval of 5 years. In the United States, the guidelines for management of abnormal cervical cytology advised against repeating smears based only on the absence of endocervical cells, but clinicians may decide to perform an additional smear after 1 year, before return to the regular program of 3-year intervals.10 In Europe, an additional smear is not generally advised, but most countries advise an additional smear under specific conditions, such as first smears or follow-up smears. The presence of cells from the transformation zone again has
been reported to be an important issue for an adequate sample.\textsuperscript{11,12}

Our aim was to compare the incidence of invasive cervical cancer and the incidence of preinvasive lesions after negative smears with and without endocervical cells. We focused specifically on the endocervical cells, but the absence of metaplastic cells, which in itself during the study period was not a reason for an additional smear in the Netherlands, also was explored. From the Dutch Network and National Database for Pathology (PALGA), we retrieved results for all cervical smears obtained for screening purpose in 1990 and 1991 and for all cytologic and histologic examinations performed before April 1998. This follow-up period of 6.25 to 8.25 years is at least 2 times longer than the recommended screening interval in the Netherlands during the study period of 3 years. Therefore, a large proportion of women with a negative smear with endocervical cells will have undergone at least 1 subsequent smear within the period studied. The large number of smears and long follow-up period allow analyzing not only histologically diagnosed CIN 1, CIN 2, and CIN 3 but also invasive cancer as an end point.

Materials and Methods

In the Netherlands, cytologic and histologic examinations are registered in a national database, PALGA, that started in 1975. From 1990 onward, more than 94% of the Papanicolaou smears and an even higher proportion of the results of histologic examinations were registered. By using the identification method used by the PALGA (4 characters of the surname, the date of birth, and the sex), the cervical screening history (rank and interval since previous smear) and follow-up data for all smears were retrieved individually.

For the present study, we retrieved data for all cervical smears (N = 1,272,558) from the PALGA obtained in 1990 and 1991. This includes a period before the reorganization of the Dutch screening program. We selected the smears registered as obtained for preventive reasons (515,146 [40.5%]); smears obtained for medical indications (5.1% of the smears) and unknown reasons (54.4% of the smears [owing to incomplete registration of the reason for the smear]) were excluded. Furthermore, preventive smears are from women who have had no positive smears during the preceding 4 years; exceptions were made for previous borderline or unsatisfactory smears, for which the negative follow-up was completed. Thus, smears that followed a positive smear within 4 years were not considered preventive but were considered follow-up smears.

For the study, we included all preventive smears that had no cervical abnormality. Smears were classified based on the registration of the item “no endocervical cells present.” The incidence of abnormalities was estimated on the basis of the highest histologically confirmed abnormality diagnosed before April 1998. Thus, women were followed up for 6.25 to 8.25 years. We considered CIN 1, CIN 2, and CIN 3 (the latter includes severe dysplasia and carcinoma in situ) and invasive cervical cancer. The preinvasive stage, CIN 1, is equal to a low-grade squamous intraepithelial lesion (LSIL), whereas CIN 2 and CIN 3 are high-grade SIL (HSIL).

The incidence of (pre-) invasive lesions after negative smears without endocervical cells was compared with that after negative smears with endocervical cells; a similar comparison was made for the difference between negative smears with and without metaplastic cells. We also estimated the difference with a multivariate logistic regression model, in which we adjusted for age (in 6 categories: <25 years, 25-34 years, 35-44 years, 45-54 years, 55-64 years, and 65 years or older) and screening history, which is a combination of the first smear (first category) and the screening interval in the case of a preceding smear (in the categories <1 year, 1-2 years, 2-3 years, 3-4 years, 4-5 years, and 5 years or longer). Both variables increased the fit of the model significantly (P < .05). We calculated odds ratios and their 95% confidence interval (95% CI) using the regression coefficients and the standard errors estimated in the model.

Results

In 1990 and 1991, 515,146 smears were registered as performed for screening purposes. Of these smears 87% were negative, of which most (88.3%) contained endocervical cells \textsuperscript{1}, \textsuperscript{12} Table 1. The proportion of negative smears without endocervical cells is relatively high at a young age (<25 years) and at an older age (65 years or older) and lowest (10%) in women between 35 and 45 years of age.

In \textsuperscript{12} Table 1 and \textsuperscript{12} Table 3, the intensity of follow-up was compared for negative smears with and without endocervical cells. The proportion of smears without endocervical cells with no follow-up registered in the study period (15%) was slightly higher compared with that for negative smears with endocervical cells (13%) (Table 2). In both groups, most women had at least 2 follow-up examinations, which gives enough opportunity to detect an abnormality. The time from a negative smear until the subsequent examination is given in Table 3. As expected, the subsequent examination after negative smears without endocervical cells was performed within a shorter interval after the initial smear: 19% of these smears had a follow-up examination registered within 1 year compared with 10% of the negative smears with endocervical cells. Within 3 years, 40% of all negative smears without endocervical cells had a follow-up examination registered, compared with 21% for negative smears with endocervical cells. Thus, the number of examinations registered after the negative smears was about equal in both
groups, but the time until follow-up was shorter for negative smears without endocervical cells.

The maximal histologic diagnosis before April 1998 is shown in Table 4. The incidence of cervical neoplasia detected after negative smears without endocervical cells was about equal to that for the smears with endocervical cells. After negative smears with endocervical cells, there were 0.54 invasive cervical cancers (n = 215) detected per 1,000 smears; after negative smears without endocervical cells, there were 0.53 invasive cervical cancers (n = 28) detected per 1,000 smears.

There was no significant difference in the incidence of any histologic categories (Table 5). When we compared the incidence of CIN 1 or worse, CIN 2 or worse, and CIN 3 or worse, again, no significant differences were found. We also adjusted the incidences for age and screening interval. The estimated odds ratios were only slightly different from those estimated in the univariate analysis. None of the analyses showed any prognostic difference between negative smears without endocervical cells and negative smears with endocervical cells; in fact, all odds ratios were very close to 1.00 (Table 5).

We also estimated the difference of cervical neoplasia between smears with and without metaplastic cells. During the study period, the absence of metaplastic cells was not an indicator for an additional smear. In our data, the proportion of smears registered as without metaplastic cells was 52%. All estimated odds ratios were less than 1, and the differences between smears with and without metaplastic cells were significant (CIN 1 or worse: odds ratio, 0.82; 95% CI, 0.77-0.87; and CIN 3 or worse: odds ratio, 0.81; 95% CI, 0.75-0.89), except for invasive cancers. Thus, in our data, the absence of metaplastic cells was not associated with a higher risk for cervical neoplasia.

**Discussion**

In our data, the histologic follow-up after a negative smear without endocervical cells was not significantly
different from that of a negative smear with endocervical cells. We estimated that the risk of an invasive cervical carcinoma within 8 years after negative smears without endocervical cells was equal to the risk after negative smears with endocervical cells (odds ratio, 1.01; 95% CI, 0.68-1.49); the same conclusion applies when CIN 1, 2, 3, or worse were used as the end point.

The intensity of follow-up could have influenced our results, as it was recommended that women with negative smears without endocervical cells undergo an additional smear after 1 year instead of the routine screening interval of 3 years in the study period. The proportion of women who had no follow-up was equal in both groups, but the average interval to the subsequent smear was slightly shorter for negative smears without endocervical cells. A more intensive follow-up could have led to an increase in sensitivity of the follow-up and, thus, to a reduced incidence of invasive cancers, owing to successful treatment of preinvasive lesions. At the same time, this should lead to a higher proportion of preinvasive lesions. In fact, the difference in intensity in follow-up was small, and the incidence of preinvasive lesions after smears without endocervical cells was not higher in our data.

In our analysis, smears were regarded as without endocervical cells when this specific category (no endocervical cells present) was selected explicitly in the cytology report on the item “endocervical cells.” Some laboratories may have used the item “quality of the smear” to indicate the cell types that were present. This would imply an incomplete analysis with possibly biased results. However, it seems that 95% of the smears, which had a quality report in which the presence of endocervical cells was not explicitly reported (4 categories), also had the registration of no endocervical cells present. Thus, the influence on the results cannot be important.

After the reorganization of the screening program in the Netherlands, much attention has been given to standardization of the screening procedures. It would be interesting to repeat the analysis when these more recent smears have a sufficient follow-up period.

In the literature, the clinical relevance of endocervical cells has been explored in different types of analyses that seemed to lead to opposite conclusions. Cross-sectional analyses described that the proportion abnormalities detected in smears without endocervical cells is lower compared with smears containing endocervical cells.1-3 To explore whether differences are due to differences in data or to differences in methods, we also subjected our data set to the cross-sectional study design, in which we found that the proportion of abnormal smears (cytologically atypical cells or worse) was

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**Table 4**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>With Endocervical Cells</th>
<th>Without Endocervical Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proportion (10^-3)</td>
<td>Number</td>
</tr>
<tr>
<td>CIN 1 (LSIL)</td>
<td>4.6</td>
<td>1,818</td>
</tr>
<tr>
<td>CIN 2 (HSIL)</td>
<td>2.2</td>
<td>870</td>
</tr>
<tr>
<td>CIN 3 (HSIL)</td>
<td>3.9</td>
<td>1,538</td>
</tr>
<tr>
<td>Invasive</td>
<td>0.54</td>
<td>215</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

* From the Dutch Network and National Database for Pathology.

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**Table 5**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN 1 (LSIL)</td>
<td>0.93 (0.81-1.07)</td>
<td>0.95 (0.83-1.09)</td>
</tr>
<tr>
<td>CIN 2 (HSIL)</td>
<td>0.99 (0.82-1.21)</td>
<td>0.97 (0.80-1.18)</td>
</tr>
<tr>
<td>CIN 3 (HSIL)</td>
<td>1.06 (0.92-1.22)</td>
<td>1.04 (0.90-1.20)</td>
</tr>
<tr>
<td>Invasive</td>
<td>0.97 (0.65-1.44)</td>
<td>1.01 (0.68-1.49)</td>
</tr>
<tr>
<td>CIN 1 or worse (LSIL +)</td>
<td>0.99 (0.91-1.08)</td>
<td>0.99 (0.91-1.08)</td>
</tr>
<tr>
<td>CIN 2 or worse (HSIL +)</td>
<td>1.03 (0.92-1.15)</td>
<td>1.01 (0.91-1.13)</td>
</tr>
<tr>
<td>CIN 3 or worse (HSIL +)</td>
<td>1.05 (0.92-1.20)</td>
<td>1.03 (0.91-1.18)</td>
</tr>
</tbody>
</table>

CIN, cervical intraepithelial neoplasia; CI, confidence interval; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

* Estimated for negative smears without endocervical cells compared with negative smears with endocervical cells. The multivariate model included age and screening history.

From the Dutch Network and National Database for Pathology.
11.5% in smears with endocervical cells, compared with only 5.7% in smears without endocervical cells, estimated for all preventive smears taken in 1990 and 1991 in the Netherlands (n = 515,146). Hence, in this respect, our results are in line with the studies previously described.¹⁻³ This shows that the apparent contradictory results from the cross-sectional study compared with the longitudinal design also are found within a data set. Theoretically, lower detection rates found in smears without endocervical cells can reflect a true lower incidence of abnormalities. This also may be caused by less complete registration of absence of endocervical cells once abnormalities are found in a smear. It is important to realize that a cross-sectional design that does not include follow-up data is not appropriate to study the prognostic relevance of endocervical status in negative smears.

Retrospective analyses, previously described, reported high proportions of (false-) negative smears without endocervical cells before the diagnosis of invasive cervical cancer.⁴⁻⁵ These differences in results between the retrospective and the prospective analyses can be explained only by differences in data or in definitions. If retrospective and prospective analyses are studying the same data from different perspectives and under similar assumptions, conclusions should be consistent. The proportion of (false-) negative smears without endocervical cells before invasive cancer has been reported to be 64% (n = 47)³ and 78% (n = 55).⁴ A serious problem with these 2 studies is that the endocervical status was assessed retrospectively during the study, without a similar assessment in controls. However, it is unclear whether this may explain the high percentages of negative smears without endocervical cells before development of invasive cancers.

Kristensen et al⁴ found that the absence of metaplastic cells was an important indicator of false-negative smears obtained before the diagnosis of invasive cancer. We found that the number of abnormalities within 6 to 8 years of follow-up after negative smear without metaplastic cells was lower compared with that for negative smear with metaplastic cells (CIN 3 or worse: odds ratio, 0.81; 95% CI, 0.75-0.89), suggesting that the absence of metaplastic cells is associated with lower risk for cervical neoplasia. However, in view of the low percentage of smears registered as containing metaplastic cells and the fact that there were no recommendations for follow-up, the usefulness of the registration in this respect is questionable.

In the present analysis, we used all invasive cancers of the uterine cervix, including squamous carcinoma and adenocarcinoma. We also estimated the incidence of these carcinomas separately to explore the differences. After a negative smear with endocervical cells, 144 squamous carcinomas (0.36 per 1,000 initially negative smears) and 65 adenocarcinomas (0.16 per 1,000 initially negative smears) were detected. For 6 cases, the morphologic features were not clearly described. After a negative smear without endocervical cells, 20 squamous carcinomas (0.38 per 1,000 initially negative smears) and 8 adenocarcinomas (0.15 per 1,000 initially negative smears) were detected. Thus, no relation between endocervical status and the proportion of squamous carcinomas or adenocarcinomas could be established.

Based on these data, we conclude that the risk of severe cervical neoplasia in the next 6 to 8 years for women who had a negative smear does not depend on endocervical status. Hence, an additional smear for women with negative smears without endocervical cells is not justified.

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References