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**Abstract:** Background: Since the introduction of the Pap smear screening, the incidence of squamous cell carcinoma (SCC) has decreased significantly, but the incidence of adenocarcinoma (AC) relative to SCC has increased. Aim: To compare the Pap smear history of patients with AC and SCC of the cervix. Methods: Patients for the study were identified from the database of Queensland Centre for Gynaecological Cancer. Patients with AC and SCC were matched for age at diagnosis and International Federation of Gynecology and Obstetrics stage. The final population included 188 matched pairs, being 376 patients in total. Data were collected upon the histological type of cancer, result of the most recent Pap smear, date and result of the Pap smear prior to the most recent Pap smear and symptoms. Chi-squared tests and Fisher’s exact test were used to compare the two patient groups for several variables. Results: Patients with AC had significantly more false-negative results on their most recent Pap smear (P < 0.0001) than patients with SCC. The incidence of symptoms such as bleeding and/or vaginal discharge was comparable in patients with AC and SCC. The time between the most recent Pap smear and the diagnosis of cervical cancer was significantly shorter for patients with AC (P = 0.01). Conclusions: Patients with AC had Pap smears more regularly than those with SCC, and their most recent Pap smear was significantly more likely to be normal. Thus, Pap smear prior to a diagnosis of AC is more likely than SCC false-negative and therefore not indicative of cervical cancer.
Title:

Pap smear screening history of women with squamous cell carcinoma and adenocarcinoma of the cervix

Short title:

Comparison of screening history of cervical cancer patients

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Pap smear screening history of women with squamous cell carcinoma and adenocarcinoma of the cervix

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Abstract

Background: Since the introduction of the Pap smear screening, the incidence of squamous cell carcinoma (SCC) has decreased significantly but the incidence of adenocarcinoma (AC) relative to SCC has increased. The result of AC false-negative screening test has been higher than that of SCC.

Aim: To compare the Pap smear history of patients with AC and SCC of the cervix.

Methods: Patients for the study were identified from the database of Queensland Centre for Gynaecological Cancer. Patients with AC and SCC were matched for age at diagnosis and FIGO stage. The final population included 188 matched pairs, being 376 patients in total. Data were collected upon the histological type of cancer, age at diagnosis, FIGO stage, result of the most recent Pap smear, date and result of the Pap smear prior to the most recent Pap smear and symptoms. Chi square test and Fisher’s exact test were used to compare the two patient groups for several variables.

Results: Patients with AC had significantly more false-negative results on their most recent Pap smear \( (P < 0.0001) \) than patients with SCC. The incidence of symptoms such as bleeding and/or vaginal discharge was comparable in patients with AC and SCC. The time between the most recent Pap smear and the diagnosis of cervical cancer was significantly shorter for patients with AC \( (P = 0.01) \).

Conclusions: Patients with AC had Pap smears more regularly than those with SCC and their most recent Pap smear was significantly more likely to be normal. Thus, PAP smear prior to a diagnosis of AC is more likely than SCC negative and therefore not indicative of cervical cancer.

Key words: cervical cancer, Pap smear, squamous cell carcinoma, adenocarcinoma, screening history.
Introduction

The Pap smear screening test is the most cost-effective cancer screening method available\(^1\) with an estimated over 90% effectiveness by detecting early changes in the cells of the cervix.\(^2\) As a result, the incidence of all cervical cancers declined from 13.4 per 100,000 women of all ages in 1990 to 7.3 in 2001.\(^3\) Throughout the same time period the mortality from cervical cancer for women of all ages decreased by 56%.\(^3\)

The majority of women are diagnosed with squamous cell carcinoma (SCC). Since the introduction of the Pap test screening, the incidence of SCC has declined dramatically while the incidence of adenocarcinoma (AC) relative to SCC has increased.\(^4-8\) In Australia, the incidence of SCC has almost halved since 1990 while there was hardly any reduction for AC.\(^3\) In 1990, AC accounted for 16.3% of all new cases of cervical cancer in women aged 20-69 years whereas it was 20.0% in 2001.\(^3\)

Current literature suggests that patients with SCC have a reduced frequency of screening compared to healthy women,\(^9,10\) while patients with AC in situ appear to have a screening history similar to healthy women.\(^11\) However, no previous study has undertaken a direct comparison of the screening history of patients with AC and SCC. Accordingly, this study was carried out to directly compare the Pap smear screening history of patients with AC and SCC.
Methods

Patients
A total of 3412 cases of invasive cervical cancer are currently registered at the data base of the Queensland Centre for Gynaecological Cancer (QCGC) in Brisbane, Australia. For the aim of this study patients had to fulfil the following inclusion criteria: patients had to have treatment for primary cervical cancer (AC or SCC) at one of the hospitals associated with QCGC, patients had to be between 20 and 70 years of age at diagnosis and diagnosed between January 1996 and January 2006. Two hundred sixteen patients with AC and 754 patients with SCC met those inclusion criteria. Then each patient with AC was matched with a patient with SCC for FIGO stage and age at diagnosis, resulting in 204 pairs of patients. A further 20 patients were excluded after histopathological review for the following reasons: the histological type of their cancer appeared not to be of cervical origin (n=3); their last couple of Pap smears were for non-screening purposes (n=12); absence of screening records because they were referred from abroad (n=3); it appeared to have a recurrent carcinoma (n=1); and one was a double match-up. Finally, analysis was based on the data of 376 patients, being 188 AC/SCC paired patients matched for FIGO stage of cancer and age at diagnosis. This study has been approved by The Royal Brisbane Hospital Human Research Ethics Committee (Brisbane, Australia).

Pap smear history
The Pap smear screening history of these patients was obtained and two key events were considered. The first event was the most recent Pap smear prior to or on the date of diagnosis. This Pap smear was defined as $P_0$. The second event considered was the
Pap smear that was taken prior to the most recent Pap smear. This Pap smear was referred to as P1. Data collected on P0 included the result of that Pap smear. The result was categorized into normal, abnormal or no Pap smear. For the aim of this study a Pap smear was defined abnormal if the result included: possible low-grade squamous intraepithelial lesion, low-grade squamous intraepithelial lesion, possible high-grade squamous intraepithelial abnormality, high-grade squamous intraepithelial lesion, squamous cell carcinoma, atypical endocervical cell of undetermined significance, atypical glandular cells of undetermined significance, possible high-grade glandular lesion, endocervical adenocarcinoma in-situ, adenocarcinoma (Terminology of the Australian Modified Bethesda System, AMBS 2004). Data collected on P1 included the result and date of that Pap smear. The result was defined in the same way as that of P0. That date was used to calculate the length of time between P1 and the date of diagnosis. In accordance with the current PAP smear screening guidelines, the length of time was divided into four categories: 2 years; 2 to 5 years; over 5 years and no Pap smear.

Several patients were found to have had a Pap smear with an unsatisfactory result. In a normal course of action these patients would have a repeat smear after 6-12 weeks. If such a satisfactory repeat Pap smear was taken the result and date of that Pap smear were used. In other cases, however, no record of a repeat smear could be found in which case the date and result of that Pap smear was classified as unknown. Also some patients had several repeat Pap smears in a short period of time prior to the date of diagnosis. In this case the most recent Pap smear prior to date of diagnosis was considered as P0 while the Pap smear prior to this series of Pap smears was treated as P1.
The Pap smears used were conventional slide Pap smears rather than a liquid-based technique. The data on Pap smear history were collected out of various resources which included the database of the QCGC, patient charts and pathology reports from multiple pathology centres. PAP smears were not retrieved and re-screened for the aim of this study.

**Symptoms at diagnosis**

Data were collected on patients’ symptoms at diagnosis. Those symptoms were categorized into six groups: no symptoms; bleeding (postcoital, intermenstrual or postmenopausal); vaginal discharge; bleeding and vaginal discharge; other symptoms, and symptoms unknown. The data were collected from the database of the QCGC and from the patient charts.

**Statistical analysis**

Statistical analysis has been carried out using SPSS (Statistical Package for Social Sciences, version 14.0). Standard descriptive statistical procedures were applied to obtain frequencies and percentages. The Chi-square test was the principal test used in the statistical analysis to compare the two patient groups for several variables. However, in cases where the Chi-square test was inappropriate due to small cell numbers, the Fisher’s exact test was applied.
Results

Patients mean age was 41 years (range, 22-70 years). Almost exact matching was obtained for the 188 pairs of patients in regards to age and stage (Table 1).

Overall, 157 patients (41.8%) had been screened within the previous 2 years. Patients with AC were significantly more likely having had a Pap smear screening test within the previous 2 years. Patients with SCC were more likely that the most recent Pap smear screening test was more than 5 years ago ($P < 0.0001$, Table 2). Sixty-three patients (16.8%) had no smears recorded prior to or at P0, and false-negative results for patients with AC and SCC were recorded in 9 (5.6%) and 2 patients (1.3%) prior to or at P0, respectively ($P <0.0001$) (Table 2).

Of the 376 patients, 210 patients (55.9%) denied any symptoms, whereas 122 patients (32.4%) reported bleeding and another 29 patients (7.7%) reported vaginal discharge. The incidence of those symptoms was similar in patients with AC and SCC.
Discussion

Compared to patients with cervical SCC, patients with AC are more likely to have regular PAP smears. However, the rate of false-negative PAP smears is higher in AC, thus indicating this screening test is more likely to fail diagnosis of cervical AC. Currently, AC accounts for 20% of all cervical cancers and its incidence relative to SCC is steadily increasing. While screening resulted in a decrease of SCCs this was not the case for ACs.

This retrospective matched case control study provides two important observations relevant to the current screening program. Firstly, patients with AC were more compliant and had their Pap smears more regularly than patients with SCC. Nearly half of AC patients (45.7%) had complied with recommended screening while only 37.8% of SCC patients followed the current PAP smear screening guidelines. Although comparison with healthy women is not available from the current study, our findings of better compliance rate among patients with AC are consistent with previous studies. Mitchell and colleagues reported a screening history similar to that of healthy controls for patients with AC. Stuart and co-workers conducted a failure analysis of cervical cancer screening among women with invasive cervical cancer. They found that 31.8% patients with SCC were never screened whereas it was 23.5% for patients with AC. For the under-screened category, it was 17.9% and 5.7% for SCC and AC, respectively. Lacey et al. reported that 51.6% women with AC had their most recent screening within 12-23 months versus 47.5% for SCC patients. Inversely, 41.1% AC patients had the most recent Pap smear over 2 years versus 46% for SCC women.

Secondly, the current Pap smear technique is less effective in detecting AC than it is in detecting SCC as the incidence of false-negative smears in the AC...
group was higher than in the SCC group. This finding is consistent with the current literature\textsuperscript{16,17}. Stuart and colleagues report on data from Alberta, Canada that patients with AC were less likely that they were never screened but had a 36\% higher rate of false-negative smears prior to diagnosis\textsuperscript{12}. As the incidence of obscuring blood and/or vaginal discharge was similar between SCC and AC, a detection error seems to be unlikely. However, it has been shown that a significant number of cervical AC arise above the level of the transformation zone or growing beneath the surface sparing the surface mucosa \textsuperscript{18}. These ACs may display an endophytic growth pattern, thus escaping cervical cytology.

The strength of the current study lies in the matching of patients with AC and SCC for age at diagnosis and FIGO stage. This makes it possible to conduct a fair comparison between the two groups. On a more cautious note, our study has 69 missing screening history taken prior to the most recent Pap smear in addition to the relatively small number of patients for each carcinoma.

In the public opinion, cervical cancer is often regarded as a disease of the promiscuous who fail to attend the regular PAP smear screening tests. This study shows that patients with AC do comply with the PAP smear screening intervals but the conventional PAP smear does not seem to diagnose AC as accurately as SCC. It cannot be ruled out that the new LBC could provide the solution to better detecting of AC. However, it is still hard to advocate that claim due to the conflicting results\textsuperscript{19,20}. The fact that the incidence of AC has not changed much since the advent of PAP smear screening suggests that new and better ways of diagnosing AC have to be found. It includes the upgrade of applied cytologic research to improve the sensitivity to detect the precursor lesions of AC. Other well established risk factors responsible for cervical carcinoma need to be included for further studies.
Acknowledgements

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References:


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<tr>
<th>Age at diagnosis (years)</th>
<th>Total</th>
<th>AC</th>
<th>SCC</th>
</tr>
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<tbody>
<tr>
<td>20-29</td>
<td>32 (8.5)</td>
<td>16 (8.5)</td>
<td>16 (8.5)</td>
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<tr>
<td>30-39</td>
<td>137 (36.4)</td>
<td>69 (36.7)</td>
<td>68 (36.2)</td>
</tr>
<tr>
<td>40-49</td>
<td>99 (26.3)</td>
<td>49 (26.1)</td>
<td>50 (26.6)</td>
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<td>50-59</td>
<td>77 (20.5)</td>
<td>39 (20.7)</td>
<td>38 (20.2)</td>
</tr>
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<td>60-69</td>
<td>31 (8.3)</td>
<td>15 (8.0)</td>
<td>16 (8.5)</td>
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<table>
<thead>
<tr>
<th>FIGO stage</th>
<th>Total</th>
<th>AC</th>
<th>SCC</th>
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</thead>
<tbody>
<tr>
<td>IA</td>
<td>110 (29.3)</td>
<td>55 (29.3)</td>
<td>55 (29.3)</td>
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<tr>
<td>IB</td>
<td>216 (57.4)</td>
<td>108 (57.4)</td>
<td>108 (57.4)</td>
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<td>II</td>
<td>30 (8.0)</td>
<td>15 (8.0)</td>
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<tr>
<td>III</td>
<td>16 (4.3)</td>
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<td>IV</td>
<td>4 (1.1)</td>
<td>2 (1.1)</td>
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<tr>
<td>Total</td>
<td>376 (100)</td>
<td>188 (100)</td>
<td>188 (100)</td>
</tr>
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</table>

Data are presented as n (%) unless otherwise stated.

AC, adenocarcinoma; SCC, squamous cell carcinoma.
Table 2 Breakdown of screening history taken prior to the most recent Pap smear by histological type of carcinoma

<table>
<thead>
<tr>
<th>Screening history</th>
<th>Total</th>
<th>AC (100)</th>
<th>SCC (100)</th>
<th>χ²</th>
<th>P value</th>
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<tr>
<td>Total</td>
<td>376 (100)</td>
<td>188 (100)</td>
<td>188 (100)</td>
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<tr>
<td>P1† within</td>
<td></td>
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<tr>
<td>2 years</td>
<td>157 (41.8)</td>
<td>86 (45.7)</td>
<td>71 (37.8)</td>
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<tr>
<td>2-5 years</td>
<td>55 (14.6)</td>
<td>35 (18.6)</td>
<td>20 (10.6)</td>
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<td></td>
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<tr>
<td>Over 5 years</td>
<td>80 (21.3)</td>
<td>31 (16.5)</td>
<td>49 (26.1)</td>
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<tr>
<td>No history</td>
<td>84 (22.3)</td>
<td>36 (19.2)</td>
<td>48 (25.5)</td>
<td>24.03</td>
<td>&lt;0.0001</td>
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<tr>
<td>P0</td>
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<tr>
<td>Normal</td>
<td>11</td>
<td>9</td>
<td>2</td>
<td></td>
<td></td>
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<tr>
<td>Abnormal</td>
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<td>151</td>
<td>151</td>
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<tr>
<td>Nil</td>
<td>63</td>
<td>28</td>
<td>35</td>
<td>25.9</td>
<td>&lt;0.0001</td>
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<tr>
<td>P1</td>
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<td>Normal</td>
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<td>114</td>
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<tr>
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<td>26</td>
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<tr>
<td>Nil</td>
<td>84</td>
<td>36</td>
<td>48</td>
<td>4.52</td>
<td>0.104</td>
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</tbody>
</table>

Data are presented as n (%) unless otherwise stated.

AC, adenocarcinoma; SCC, squamous cell carcinoma.

†P1, Pap smear taken prior to the most recent one.