Risk of invasive cervical cancer after atypical glandular cells in cervical screening: nationwide cohort study

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ABSTRACT

OBJECTIVES
To investigate the risks of invasive cervical cancer after detection of atypical glandular cells (AGC) during cervical screening.

DESIGN
Nationwide population based cohort study.

SETTING
Cancer and population registries in Sweden.

PARTICIPANTS
3 054 328 women living in Sweden at any time between 1 January 1980 and 1 July 2011 who had any record of cervical cytological testing at ages 23-59. Of these, 2 899 968 women had normal cytology results at the first screening record. The first recorded abnormal result was atypical glandular cells (AGC) in 14 625, high grade squamous intraepithelial lesion (HSIL) in 65 633, and low grade squamous intraepithelial lesions (LSIL) in 244 168.

MAIN OUTCOME MEASURES
Cumulative incidence of invasive cervical cancer over 15.5 years; proportion of invasive cervical cancer within six months of abnormality (prevalence); crude incidence rates for invasive cervical cancer over 0.5-15.5 years of follow-up; incidence rate ratios compared with women with normal cytology, estimated with Poisson regression adjusted for age and stratified by histopathology of cancer; distribution of clinical assessment within six months after the abnormality.

RESULTS
The prevalence of cervical cancer was 1.4% for women with AGC, which was lower than for women with HSIL (2.5%) but higher than for women with LSIL (0.2%); adenocarcinoma accounted for 73.2% of the prevalent cases associated with AGC. The incidence rate of invasive cervical cancer after AGC was significantly higher than for women with normal results on cytology for up to 15.5 years and higher than HSIL and LSIL for up to 6.5 years. The incidence rate of adenocarcinoma was 61 times higher than for women with normal results on cytology in the first screening round after AGC, and remained nine times higher for up to 15.5 years. Incidence and prevalence of invasive cervical cancer was highest when AGC was found at ages 30-39. Only 54% of women with AGC underwent histology assessment within six months, much less than after HSIL (86%). Among women with histology assessment within six months, the incidence rate of cervical cancer after AGC was significantly higher than that after HSIL for up to 6.5 years.

CONCLUSIONS
AGC found at cervical screening is associated with a high and persistent risk of cervical cancer for up to 15 years, particularly for cervical adenocarcinoma and women with AGC at age 30-39. Compared with the reduction in risk of cancer seen after HSIL management, management of AGC seems to have been suboptimal in preventing cervical cancer. Research to optimise management is needed, and a more aggressive assessment strategy is warranted.

Introduction
Cervical screening with cytology has been implemented for decades in developed countries. By following and treating abnormalities detected at screening, the incidence of cervical cancer has been considerably reduced.1 2 The risk of cervical cancer associated with abnormalities in cervical glandular cells remains uncertain about the risk associated with abnormalities in cervical glandular cells.

Atypical glandular cells (AGC) are cytological abnormalities diagnosed when glandular cells exhibit changes but lack the features of adenocarcinoma in situ or invasive adenocarcinoma in the cervix uteri. The terminology was defined and modified by the Bethesda system, from “atypical glandular cell of undetermined significance” to “atypical glandular cells,” including subcategory specifications.5 8 Sweden has used only “atypical glandular cells” without subcategories. This is an uncommon cytological diagnosis that generally comprises less than 1% of results of cervical smear tests8 but potentially reflects a wide range of conditions. Clinical studies investigating histological results in women with a diagnosis of AGC found that it included the whole range from benign changes and...
cervical precursor lesions of glandular or squamous origin to invasive cervical cancer and other gynaecological cancers. No studies, however, have investigated the long term risk of cervical cancer after AGC by age at cytological detection and the histopathological characteristics of such cancers.

As the incidence of cervical adenocarcinoma has not decreased to the same extent as the incidence of cervical squamous cell cancer in many countries, we need evidence on the magnitude of the risks of cervical adenocarcinoma associated with AGC and research on whether the current clinical assessment after AGC reduces the risk of cervical cancer as much as the standard assessment for high grade squamous intraepithelial lesion (HSIL) or low grade squamous intraepithelial lesion (LSIL) does. We therefore used registry linkages of Swedish national data to investigate the prevalence and long term risk of invasive cervical cancer after AGC, with focus on histopathology of cancer, and cancer risk after clinical assessment.

Methods
Swedish national cervical screening programme
Cervical screening was introduced in Sweden in the 1960s, and the organised screening programme started in the 1970s. The programme invites all women aged 23-50 living in Sweden to screening every three years and those aged 51-60 every five years. In 2012, more than 90% of invited women had participated in the programme at least once in the past six years. Since 1969, the Swedish National Cervical Screening Registry (NKCx) collects all cervical screening records from the whole country, including organised and opportunistic screening tests, as well as the subsequent histology test results. Screening records for counties are successively available from 1971, and the registry is complete for all of Sweden since 1995.

Study population and data collection
This population based cohort study included all women who lived in Sweden and had any record of cervical cytological test at ages 23-59 at any time from 1 January 1980 to 1 July 2011. We excluded from the study population women who had a diagnosis of invasive cervical cancer or a total hysterectomy before their first cytology record (fig 1).

We used the screening registry to identify the study population, as well as dates and diagnoses of cytology and subsequent histology tests. The date and histopathology type of identified invasive cervical cancer was retrieved from the Swedish National Cancer Register, which contains data on all diagnoses of cancer in Sweden since 1958. Information on total hysterectomy, emigration, and death were retrieved from the Swedish Patient Register, Population Register, and Causes of Death Register, respectively. All data were linked via the unique Swedish personal identification number and then anonymised by Statistics Sweden.

Classification of cytology, cervical cancer, and clinical assessment
Cytological diagnoses were classified according to the Systematized Nomenclature of Medicine (SNOMED) code system defined by Swedish Association for Clinical

Fig 1 | Details on study inclusions and exclusions. As 207 754 women had both normal and abnormal cytology, sum of normal, abnormal, and having other abnormalities exceeded 3 024 340 women. Other abnormalities included “atypical cells of uncertain origin,” “adenocarcinoma in situ,” “adenocarcinoma,” and dysplasia with concurrent AGC and HSIL/LSIL.
Cytology (appendix 1, table A). Besides normal smear results, each woman’s first abnormal result in the data material was categorised into “AGC,” “high grade squamous intraepithelial lesions (HSIL)” or “low grade squamous intraepithelial lesions (LSIL).” HSIL included suspected high grade squamous dysplasia, moderate to severe squamous dysplasia, and cytological detection of squamous cell cancer. LSIL included atypical squamous cells of undetermined significance and mild squamous dysplasia. Women who had concurrent squamous cell dysplasia at AGC were classified as “other abnormality” and were censored in the analysis as these findings were not representative of AGC alone. Those who had abnormalities other than these described types, including “atypical cells of uncertain origin,” “adenocarcinoma in situ,” and “adenocarcinoma,” were also classified as “other abnormality” and censored. Cytology tests with inadequate quality were ignored as they were usually followed by an immediate repeat test.

We used ICD-7 (international statistical classification of diseases, seventh revision) code 171 to identify invasive cervical cancer, and the WHO/HS/Canc/24.1 histology code for anatomical location to separate squamous cell cancer and adenocarcinoma. Cases of invasive cervical cancer (98% histologically verified) after an abnormal cytology result were classified as “prevalent” if the cancer was diagnosed within six months after the abnormality or “incident” if it occurred after six months. The six month cut off was based on the observed distribution of time between cytology and histology, which was stable in our material (appendix 2, fig A). We studied the cervical cancer of all histopathological types as well as adenocarcinoma and squamous cell cancer separately.

We characterised clinical assessment within six months after abnormalities in a subcohort of women whose first abnormal result was from 1 January 1993 onwards, when histology records were complete nationwide (fig 1). Clinical assessments included history follow-up, cytology only, and no morphological follow-up.

Statistical analyses
We plotted cumulative incidence of invasive cervical cancer over 15.5 years after AGC, HSIL, and LSIL by histopathological types, based on Kaplan-Meier estimates of the survival function. We assessed the proportion of prevalent cervical cancer within each group by calculating the percentage of women with a diagnosis of cervical cancer within six months after their first detected abnormality. The analyses were stratified by age at onset of the abnormality, grouped as age 23-29, 30-39, 40-49, and 50-59, and by histopathological type of cervical cancer. We compared the proportion of prevalent cancers at the cytological finding of AGC across age groups, as well as to the corresponding measures for HSIL and LSIL, using Pearson’s χ² tests.

We used a cohort approach to assess the risk for incident cervical cancer after AGC/HSIL/LSIL, with women with normal cytology as the comparison group. Women entered the cytologically normal cohort at the time of the first cytology record if the result was normal, and contributed to the cytologically normal risk time as long as they underwent screening and had only normal cytology results. Duration of screening was defined as a maximum of five years after each normal smear result, to provide risk estimates relative to a well screened cytologically normal population. The cytologically normal risk time was censored once women had their first abnormal result. Abnormalities of AGC, HSIL, or LSIL in women who did not receive a diagnosis of prevalent cervical cancer within six months contributed to the AGC/HSIL/LSIL risk time from the beginning of the seventh month and continued to contribute to the same abnormal group regardless of the cytological findings of subsequent tests. Women were followed until a diagnosis of invasive cervical cancer, 15.5 years after the abnormality, total hysterectomy, emigration, death, or 31 December 2011, whichever came first (appendix 2, fig B).

We calculated crude incidence rates for cervical cancer diagnosed more than six months after AGC, HSIL, and LSIL by follow-up time. We used Poisson regression to estimate incidence rate ratios and 95% confidence intervals for incident cervical cancers after an abnormality at 0.5-3.5, 3.5-6.5, 6.5-10.5, and 10.5-15.5 years, compared with the incidence among women who were well screened and had only normal cytology results, with adjustment for age with a spline term, and stratification by histopathology of cancer. To assess differences by age at abnormality, we calculated incidence rate ratios for AGC for specific age groups by introducing an interaction term with age at abnormality onset.

In the subcohort of women with an abnormal result from year 1993 onwards, we assessed the distribution of clinical assessment approaches within six months after the abnormality. Among women with histology assessment, we compared the prevalence of cervical cancer at AGC with HSIL and LSIL using Pearson’s χ² tests, and estimated incidence rate ratios of incident cervical cancer after AGC compared with HSIL and LSIL using Poisson regression.

Data management and statistical analyses were performed with SAS statistical package version 9.4. Plots were generated with R version 3.1.1.

Patient involvement
No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants or the relevant patient community.

Results
Study participants
A total of 3 054 328 women were identified with a record of cytological screening in Sweden at ages 23-59 between 1 January 1980 and 1 July 2011. Of those, we excluded 29988 women because they had a diagnosis of invasive cervical cancer or received a total hysterectomy before the first screening record. In total, 3 024 340...
women entered the cohort (fig 1), of whom 14 625 women had AGC as the first abnormal cytology, 65 633 women had HSIL, and 244 168 had LSIL. The mean follow-up time among women with and without abnormal cytology was similar (table 1).

The median age at AGC was 45, significantly higher than the median age at HSIL (P < 0.001) and LSIL (P < 0.001). There were 330 cases of invasive cervical cancers diagnosed after AGC. The proportion of prevalent cervical cancer was 60%, lower than after HSIL (82%, P < 0.001) and higher than after LSIL (32%, P < 0.001). Most cervical cancers after AGC were adenocarcinoma (74%), whereas most cancers after HSIL and LSIL (>80%) were squamous cell cancer (table 1).

Cumulative incidence of cervical cancer
Cumulative incidence of invasive cervical cancer among women who had AGC increased drastically in the first six months and continued to increase steadily during follow-up, reaching 2.6% at 15.5 years (95% confidence interval 2.3% to 2.9%). The increasing pattern was similar to HSIL and LSIL, but the cumulative incidence was lower than that after HSIL (3.3%, 3.2% to 3.4%) and higher than LSIL (0.7%, 0.7% to 0.8%). The cumulative incidence of adenocarcinoma among women with AGC reached 1.9% at 15.5 years, which was considerably higher than for women with HSIL or LSIL, whereas the cumulative incidence of squamous cell cancer (0.6%) was significantly lower than HSIL but similar to LSIL (fig 2).

Proportion of prevalent cervical cancer
Among women with AGC, 1.4% had prevalent cervical cancer detected within six months. The proportion was lower than that for HSIL (2.5%, P < 0.001), but more than six times higher than that for LSIL (0.2%, P < 0.001). Most prevalent cancers at AGC were adenocarcinoma (73.2%), and the highest proportions of prevalent cervical cancer at diagnosis of AGC were found in the age group 30-39 (2.3%), both for adenocarcinoma (P < 0.001) and squamous cell cancer (P < 0.001), for age groups 30-39 versus 50-59. Conversely, most prevalent cancers at HSIL were squamous cell cancers (86.8%), and the highest proportion of prevalent cancer at diagnosis of HSIL was found in age group 50-59 (5.0%). Prevalent cancer at diagnosis of LSIL was fairly uncommon (0.2%) and did not vary much with age (table 2).

Risk for incident cervical cancer
The incidence rate of cervical cancer after AGC was high at the beginning of follow-up, at 329 per 100 000 person years in the first year, and decreased with time but was still higher than after HSIL for up to around six years and notably higher than after LSIL for up to 10 years (fig 3). Compared with women with normal cytology results, presence of AGC implied a significantly increased risk of cervical cancer for up to 15.5

Table 1 | Characteristics of study participants and numbers of cervical cancers, with percentage among all cervical cancers in parentheses, by cytological findings

| Abnormality | AGC | HSIL | LSIL | Normal |
|-------------|-----|------|------|--------|
| No of women | 14 625 | 65 633 | 244 168 | 2 899 968 |
| Median age (years) at abnormality | 45 | 33 | 33 | NA |
| Total person years (×1000 person years) | 146.9 | 664.8 | 2 429.7 | 39 009.9 |
| Mean follow-up (years) | 9.9 | 9.8 | 10.0 | 11.1 |
| No of cervical cancers, all histopathology | 330 | 2004 | 1328 | 3 042 |
| No of cervical adenocarcinomas (% among all cervical cancers) | 243 (73.6) | 218 (10.9) | 193 (14.5) | 877 (28.8) |
| No of cervical squamous cell cancers (% among all cervical cancers) | 74 (22.4) | 1717 (85.7) | 1091 (82.2) | 2 018 (66.3) |
| No of prevalent cervical cancers (% among prevalent cervical cancers) | 198 (60.0) | 1 633 (81.5) | 428 (32.2) | NA |
| No of prevalent adenocarcinomas (% among prevalent cervical cancers) | 145 (73.2) | 163 (10.0) | 49 (11.4) | NA |
| No of prevalent squamous cell cancers (% among prevalent cervical cancers) | 44 (22.2) | 1418 (86.8) | 368 (86.0) | NA |
| No of incident cervical cancers (% among all cervical cancers) | 132 (40.0) | 371 (18.5) | 900 (67.8) | NA |
| No of incident adenocarcinomas (% among all cervical cancers) | 98 (74.2) | 55 (14.8) | 144 (16.0) | NA |
| No of incident squamous cell cancers (% among all cervical cancers) | 30 (22.7) | 299 (80.6) | 723 (80.3) | NA |

AGC = atypical glandular cells; HSIL = high grade squamous intraepithelial lesion; LSIL = low grade squamous intraepithelial lesion. 

Fig 2 | Cumulative incidence of cervical cancer after AGC, HSIL, and LSIL, by histopathology of cancer

Cumulative incidence of squamous cell cancer
Cumulative incidence of adenocarcinoma

All types

AGC HSIL LSIL

Abnormality

Follow-up (years)

0 2 4 6 8 10 12 14 16

Cumulative incidence (%)
The incidence rate ratio for any cervical cancer after AGC, relative to women with normal cytology, was close to twofold significantly higher than the corresponding incidence rate ratio after HSIL in the first two screening rounds of 0.5-6.5 years after the abnormality (table 3).

The incidence rate of adenocarcinoma after AGC was considerably higher than that after HSIL and LSIL throughout 15.5 years, while it was generally lower for squamous cell cancer (fig 3). The incidence rate ratios showed an 61-fold increased risk of adenocarcinoma after AGC compared with women with normal cytology in the first screening round (60.8, 95% confidence interval 46.0 to 80.4) and remained ninefold higher for up to 15.5 years (table 3). These incidence rate ratios for adenocarcinoma were significantly higher than those associated with HSIL and LSIL for up to 10.5 years (table 3).

Notably, the ratio of adenocarcinoma after AGC was significantly higher than the ratio of squamous cell cancer after HSIL for up to 10.5 years (table 3).

Age was an effect modifier for the incidence rate ratio of incident cervical cancer after AGC compared with women with normal cytology (Wald test of interaction term with age at onset: P = 0.017). Women with AGC at ages 30-39 had the highest incidence rate and incidence rate ratio compared with those with normal cytology results for all types of cervical cancer (fig 3). The incidence rate ratios showed an 61-fold increased risk of adenocarcinoma after AGC compared with women with normal cytology in the first screening round (60.8, 95% confidence interval 46.0 to 80.4) and remained ninefold higher for up to 15.5 years (table 3). These incidence rate ratios for adenocarcinoma were significantly higher than those associated with HSIL and LSIL for up to 10.5 years (table 3). Notably, the ratio of adenocarcinoma after AGC was significantly higher than the ratio of squamous cell cancer after HSIL for up to 10.5 years (table 3).

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Clinical assessment after abnormalities

Of women with AGC, 53.8% were followed up with histology assessment within six months, which was significantly lower than the proportion of histology assessment after HSIL (85.9%, P<0.001) but higher than that after LSIL (43.2%, P<0.001) (table 5). Among women with histology assessment, the proportion with

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**Table 2 | Prevalence of cervical cancer at AGC, HSIL, and LSIL, by age (years) at detection abnormality and histopathology of cancer**

| Age (years) | AGC | | HSIL | | LSIL |
|-------------|-----|-----|-----|-----|-----|
| All ages    | 198 | 1.35 | 1633 | 2.49 | 428 | 0.18 |
| 23-29       | 18  | 1.22 | 197  | 0.82 | 78  | 0.08 |
| 30-39       | 75  | 2.29 | 663  | 2.84 | 155 | 0.23 |
| 40-49       | 70  | 1.30 | 489  | 3.92 | 124 | 0.24 |
| 50-59       | 35  | 0.78 | 284  | 5.01 | 71  | 0.23 |

| All histopathologies | Adenocarcinoma | Squamous cell cancer |
|----------------------|----------------|---------------------|
| All ages             | 184            | 44                  |
| 23-29                | 11             | 6                   |
| 30-39                | 51             | 20                  |
| 40-49                | 54             | 14                  |
| 50-59                | 29             | 4                   |

*Percentage of prevalent cancer among women with abnormality.

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Table 3 | Event counts, incidence rates, and incidence rate ratios (95% confidence intervals) for incident cervical cancer by abnormality, follow-up time (years), and histopathology of cancer

| Abnormality | 0.5-3.5 years | 3.5-6.5 years | 6.5-10.5 years | 10.5-15.5 years |
|-------------|---------------|---------------|----------------|----------------|
|              | No of cases | IR† | IRR (95% CI)† | No of cases | IR† | IRR (95% CI)† | No of cases | IR† | IRR (95% CI)† | No of cases | IR† | IRR (95% CI)† |
| All histopathologies | | | | | | | | | | | | | |
| AGC | 73 | 190.8 | 24.1 (19.1 to 30.5) | 26 | 79.3 | 10.0 (6.8 to 14.7) | 21 | 58.7 | 7.4 (6.8 to 11.4) | 12 | 37.9 | 4.8 (2.7 to 8.5) |
| HSIL | 178 | 103.9 | 13.4 (11.5 to 15.6) | 58 | 40.1 | 5.1 (4.0 to 6.7) | 72 | 45.4 | 5.8 (4.6 to 7.3) | 63 | 43.6 | 5.5 (4.3 to 7.1) |
| LSIL | 347 | 52.9 | 6.8 (6.1 to 7.6) | 193 | 35.5 | 4.5 (3.9 to 5.3) | 192 | 33.2 | 4.2 (3.7 to 4.9) | 168 | 33.4 | 4.2 (3.6 to 5.0) |
| Normal | — | — | Reference | — | — | Reference | — | — | Reference | — | — | Reference |
| Adenocarcinoma | | | | | | | | | | | | | |
| AGC | 53 | 138.6 | 60.8 (46.0 to 80.4) | 22 | 671 | 29.0 (19.0 to 44.4) | 16 | 44.7 | 19.2 (11.7 to 31.5) | 7 | 22.1 | 9.4 (4.5 to 19.9) |
| HSIL | 25 | 14.6 | 6.8 (4.6 to 10.2) | 7 | 4.8 | 2.2 (1.0 to 4.7) | 12 | 7.6 | 3.4 (1.9 to 6.0) | 11 | 7.6 | 3.3 (1.8 to 6.1) |
| LSIL | 44 | 6.7 | 3.1 (2.3 to 4.2) | 39 | 7.2 | 3.3 (2.4 to 4.5) | 31 | 5.4 | 2.4 (1.7 to 3.4) | 30 | 6 | 2.6 (1.8 to 3.8) |
| Normal | — | — | Reference | — | — | Reference | — | — | Reference | — | — | Reference |
| Squamous cell cancer | | | | | | | | | | | | | |
| AGC | 18 | 47.1 | 91.5 (57.4 to 145.5) | 4 | 12.2 | 2.4 (0.9 to 6.3) | 4 | 11.2 | 2.2 (0.8 to 5.8) | 4 | 12.6 | 2.5 (0.9 to 6.7) |
| HSIL | 145 | 86.6 | 16.3 (13.7 to 19.4) | 47 | 32.5 | 6.3 (4.7 to 8.4) | 57 | 36.0 | 7.0 (5.3 to 9.1) | 50 | 34.6 | 6.7 (5.1 to 8.9) |
| LSIL | 292 | 44.5 | 8.6 (7.6 to 9.8) | 147 | 271 | 5.2 (4.4 to 6.2) | 151 | 26.1 | 5.1 (4.3 to 6.0) | 133 | 26.4 | 5.1 (4.3 to 6.1) |
| Normal | — | — | Reference | — | — | Reference | — | — | Reference | — | — | Reference |

*No of cases of cervical cancer.
†Observed incidence rate, per 100 000 person years.
‡Incidence rate ratio with 95% confidence interval, relative to women with regular normal cytology, adjusted for attained age.

Fig 4 | Crude incidence rates of incident cervical cancers at follow-up of AGC, HSIL, and LSIL, by age at abnormality and histopathology of cancer. To avoid sparse and fluctuating data, right end point of follow-up time denotes incidence in 10.5-15.5 years.
prevalent cervical cancer at AGC (2.8%) was similar to that at HSIL (3.2%, P = 0.10) and higher than that at LSIL (0.4%, P = 0.001), while the incidence of cervical cancer after AGC continued to be higher than that after HSIL and LSIL for up to 6.5 years (table 6).

### Calendar period effect

We examined prevalent and incident cervical cancer up to 3.5 years after abnormalities, as well as the coverage of histology assessment within six months, by calendar time periods. The coverage of immediate histology assessment increased consistently over the study period for all abnormalities. Only among women with AGC, however, did we observe an increasing (although not significant) trend in incident cervical cancers over the past 30 years (appendix 1, table C).

### Discussion

Main findings and interpretations

In this national population based cohort study, we observed a considerable risk of invasive cervical cancer associated with atypical glandular cells (AGC) found at cervical cytological screening. This high risk could be due to a high underlying risk for these women or suboptimal clinical management, or both.

Our assessment of cumulative incidence of cervical cancer after AGC indicated that its risk profile was moderately lower than that of HSIL but considerably higher than that of LSIL. Adenocarcinoma was the dominant histopathological type of cervical cancer after AGC, and the risk for this disease was significantly higher than after any other cytological abnormality. To the best of our knowledge, ours is the first study to show the association between AGC and a long term increased risk of adenocarcinoma at the population level. We also found that having AGC at ages 30–39 conferred the highest risk for cervical cancer, both in terms of the proportion of prevalent cancer and the rate of incident cancer.

Clinical management can affect the risk of cancer after cytological abnormalities. Less attention has been paid to optimal management of AGC in European guidelines,20–22 and the Swedish guideline for management of abnormalities was not issued until 2010.23 We found that the proportion of prevalent cancer with AGC was lower than that with HSIL, but, given that only 54% of women with AGC were followed up with histology within six months while 86% of HSIL were, we could have underestimated prevalent cancer with AGC. In our evaluation among women who had histology assessment within six months, 2.8% of women with AGC were found to have a prevalent cancer, which was closer to

### Table 4 | Age specific event counts, incidence rates, and incidence rate ratios for incident cervical cancer (all histopathologies) after AGC relative to women with normal results on cytology, by follow-up time

| Age (years) at AGC | 0.5-3.5 years | 3.5-6.5 years | 6.5-10.5 years | 10.5-15.5 years |
|-------------------|---------------|---------------|---------------|---------------|
| No of cases* | IR† | (95% CI)‡ | No of cases* | IR† | (95% CI)‡ | No of cases* | IR† | (95% CI)‡ | No of cases* | IR† | (95% CI)‡ |
| 23-29 | 6 | 152.4 | 16.9 (8.9 to 32.3) | 2 | 61.2 | 7.2 (3.5 to 14.6) | 2 | 579 | 5.4 (2.6 to 11.3) | 0 | 0 |
| 30-39 | 24 | 274.6 | 36.7 (26.4 to 51.0) | 13 | 177.7 | 15.5 (9.8 to 24.4) | 6 | 77.7 | 11.6 (7.1 to 19.0) | 3 | 43.5 |
| 40-49 | 27 | 190.5 | 22.6 (16.1 to 31.6) | 6 | 48.9 | 9.5 (6.0 to 15.1) | 8 | 58.8 | 7.2 (4.4 to 11.7) | 4 | 32.3 |
| 50-59 | 16 | 140.4 | 19.8 (11.4 to 29.2) | 5 | 50.4 | 8.3 (5.1 to 13.7) | 5 | 45.4 | 6.3 (3.7 to 10.6) | 5 | 53.3 |

*No of cases of cervical cancer.
†Observed incidence rate, per 100 000 person years.
‡Incidence rate ratio and 95% confidence interval, relative to women with AGC, adjusted for attained age.

### Table 5 | Distribution of clinical assessment approaches within six months after detection of abnormalities

| No (%) | P value* |
|--------|----------|
| AGC    |          |
| Histology | 5748 (53.8) | Reference |
| Cytology only | 2832 (26.5) |          |
| No morphology | 2108 (19.7) |          |
| HSIL   |          |
| Histology | 39883 (85.9) | <0.001 |
| Cytology only | 3844 (8.3) |          |
| No morphology | 2696 (5.8) |          |
| LSIL   |          |
| Histology | 80318 (43.2) | <0.001 |
| Cytology only | 71240 (38.3) |          |
| No morphology | 34495 (18.5) |          |

*χ² test comparing frequency distribution of clinical assessment approaches to AGC.

### Table 6 | Prevalent and incident cervical cancer (all histopathologies) associated with AGC, HSIL, and LSIL among women with histology assessment within six months, by follow-up time

| Prevalent cancer | No of cases* | Prevalence %† | P value* |
|------------------|-------------|---------------|----------|
| AGC              | 162 | 2.8 Reference |
| HSIL             | 1288 | 3.2 | 0.10 | Reference |
| LSIL             | 311 | 0.4 | <0.001 | Reference |

*No of cases of cervical cancer.
†Percentage of having prevalent cancer among women with abnormality.
‡Observed incidence rate, per 100 000 person years.
§Incidence rate ratio and 95% confidence interval, relative to women with AGC, adjusted for age at abnormality.
¶0.9764, significant.

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the 3.2% among women with HSIL. This implies that there is a considerable proportion of invasive cervical cancer when AGC is found, and that immediate diagnostic investigation is necessary.

We also found that incidence of cancer after AGC was even higher than after HSIL in the subsequent 0.5-6.5 years and similar to HSIL for up to 10.5 years. Considering the lower coverage of histological assessment after AGC, some of the cases found in the first time period might have been missed prevalent cases. Our analysis among women who did have histology assessment within six months, however, showed that the cancer incidence after AGC was still significantly higher than after HSIL for up to 6.5 years. This suggests that there is a high risk for incident cancer that cannot be attributed to a delay in diagnostic investigation. It could be due to lesions that were missed or ineffectively eliminated during or after the initial histology. This would be particularly applicable for glandular lesions, as they might not be as visible and accessible as squamous lesions with colposcopic methods, and the treatment for glandular precursor lesions might not be as satisfactory as for its squamous counterpart. This could also partially explain the higher risk after AGC among women aged 30-39. Given that clinical assessment within six months in this age group was similar to that at other ages (appendix 1, table D), the higher risk might be the consequence of less aggressive assessment and treatment because of the desire to preserve fertility in this age group.

The coverage of immediate histology assessment has increased in the past 30 years in Sweden. Unexpectedly, the subsequent cervical cancer incidence at 0.5-3.5 years still tended to increase among women with AGC, while a similar increase was not observed for women with HSIL and LSIL. This implies there is an increasing trend in underlying risk that is not effectively suppressed by the management after AGC. The current Swedish guidelines recommend immediate histology assessment and subsequent treatment for women with AGC (similar to HSIL management) (appendix 1, table E). According to our findings, this is likely to be insufficient, and a more aggressive assessment strategy, including both an additional histology test in one year and close long term surveillance, could be considered to find the precursor lesions in time.

**Strengths and limitations of the study**

We used the Swedish National Cervical Screening Registry, which contains results of cervical screening and histology tests back to 1980. Although the registry was not nationally complete before 1995, it was complete within the counties where data were available, thus there was no selection on the characteristics of women. Together with the complete Swedish National Cancer Register, it allowed us to assess the long term risk of this rare cytological abnormality and to study particular histopathological types of cervical cancer. The ability to individually link to nationwide registers of hysterectomy, migration, and death enhanced the validity of our study by identifying true at risk groups.

Despite this, our precision was still limited because of the rarity of AGC as a cytological diagnosis, especially in some age groups, calendar periods, and histopathology findings. Although our data contain all information on histology assessment, information on exact clinical treatment of lesions was not available. Furthermore, AGC was not further specified into subcategories, and the risks of cancer after such subcategories of AGC are therefore unknown.

**Comparisons with other studies**

Several clinical studies have focused on the clinical relevance of AGC. Schnatz and colleagues reviewed 24 studies and found that 1.1% of women with AGC were confirmed as having a prevalent cervical malignancy, which was similar to the proportion of prevalent cancer in our study (1.3%). One population based register study from Taiwan found an 18-fold risk of incident cervical cancer in an average follow-up of six years after AGC, compared with the general population, which again is comparable with our results. In addition to these studies, our study provides a more specific risk assessment by follow-up time and a comparison with HSIL and LSIL, which serves to quantify the excess risk associated with AGC.

The proportion of cervical adenocarcinoma at or shortly after AGC varied between 0.6% and 3% in previous clinical studies because of limited numbers of adenocarcinoma (one to seven women). Katki and colleagues found a cumulative incidence of 1.5% for adenocarcinoma in five years after AGC in a cohort in the United States, close to our finding in the same follow-up time. Our study contained a large enough sample of women with invasive adenocarcinoma after AGC to show a significant increase in risk and provide the risk profile for an even longer follow-up time.

Others have investigated the age pattern of malignancies related to AGC, and results have been conflicting as to whether the neoplasia is more common among younger women than older, or vice versa. Our study showed that there is indeed a higher risk of cervical cancer among women with AGC aged 30-39 and that the increased risk derives mainly from increased risk of adenocarcinoma.

**Other considerations**

Testing for human papillomavirus (HPV) might improve the prediction of risk of cancer after AGC as cervical adenocarcinoma and its precursor lesions are also related to HPV infection. Ronco and colleagues showed a better adenocarcinoma prevention with primary HPV testing, which suggests a potential of this test for the detection of high risk glandular precursor lesions. A meta-analysis showed that HPV testing in women with AGC had an overall 90% sensitivity and 75% specificity for detecting CIN2+/AIS+. In the US study, 25% of women with AGCs were HPV positive, and the HPV negative AGC group had a low risk of cervical cancer in the subsequent five years. These data imply that primary HPV testing with cytology triage could select the highest risk AGC group for further clinical
assessment and treatment, although the existence of women with HPV negative AGC who develop cervical cancer warrants attention.46-48

A more aggressive assessment strategy of AGC would increase the likelihood of finding precursors such as adenocarcinoma in situ, which warrant excision of the cervical canal. This leads to an increased risk of adverse pregnancy outcomes45 as a result of cervical incompetence. As AGC is a relatively rare finding compared with, for example, HSIL (table 1), and a modest proportion of AGC (32%, data not shown) is found in women aged under 40, any increased risk of adverse pregnancy outcomes after treatment of precursors detected is likely to be limited, especially if AGC can be triaged with HPV testing. The risk of cervical incompetence and subsequent risk of, for example, premature delivery, must be weighed against the risk of development of invasive cancer if treatment of the detected precursor is delayed. Each treating physician needs to discuss this with the woman before a clinical decision is made.

Although we showed that having AGC at older ages was associated with a relatively lower risk of cervical cancer, clinical studies observed a considerable amount of endometrial cancers among women with AGC at age 50 and above,29-31 33 34 38 44-46 suggesting AGC at older ages might also be relevant for detection of endometrial cancer.

Conclusions, policy implications, and future investigations

We found that women in whom AGC was detected at cervical screening had a high proportion of prevalent cervical cancer and a higher long term risk of incident cervical cancer, especially for cervical adenocarcinoma.

Women with AGC found at screening should be properly assessed with histology immediately and must not be lost to follow-up. According to our findings, we cannot assume such women are at low risk after only one assessment. A more aggressive assessment strategy seems to be warranted, for example by including an additional histology assessment in one year and close surveillance for many years. Particular attention should be given to women aged 30-39. The rarity of AGC makes long term close surveillance feasible, in terms of administration and cost.

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Data sharing. Data from the study is available from par.sparen@ki.se.

Transparency declaration. PSp affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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1. IARC. Cervix cancer screening. In: IARC handbooks of cancer prevention. IARC Press, 2004.
2. Macgregor JE, Campbell MK, Marn EMF, Swanson KY. Screening for cervical intraepithelial neoplasia in north east Scotland shows fall in incidence and mortality from invasive cancer with concomitant rise in preinvasive disease. Br J Med 1994;308:1407-11. doi:10.1136/bmj.308.6941.1407
3. Östör AG. Natural history of cervical intraepithelial neoplasia: a critical review. Int J Gynecol Pathol 1993;12:186-92. doi:10.1097/00004347-199310000-00018
4. Gustafsson L, Adam HO. Natural history of cervical neoplasia: consistent results obtained by an identification technique. Br J Cancer 1989;60:132-41. doi:10.1038/bjc.1989.236
5. McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol 2008;9:425-34. doi:10.1016/S1470-2045(08)70103-7.
6. Solomon D. The 1998 Bethesda System for reporting cervical/vaginal cytologic diagnoses: developed and approved at the National Cancer Institute Workshop in Bethesda, MD, December 12-13, 1998. Diagn Cytopathol 1995;5:331-4. doi:10.1002/(SICI)1097-0290(199503)7:3<331::AID-DCyto100>3.0.CO;2-8.
7. Broder S. Rapid communication—the Bethesda system for reporting cervical/vaginal cytologic diagnoses—report of the 1991 Bethesda workshop. JAMA 1992;267:1892. doi:10.1001/jama.1992.03480140014005.
8. Solomon D, Davie D, Karman R, et al. Forum Group Members. Bethesda 2001 Workshop. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA 2002;287:2114-9. doi:10.1001/jama.287.16.2114.
9. Schrappe P, Guille M, O’Sullivan DM, Sorosky JJ. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 2006;107:701-8. doi:10.1097/00006252-200604000-00020.
10. Smith HO, Tiffany MF, Qualls CR, Key CR. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States—a 24-year population-based study. Gynecol Oncol 2000;78:97-105. doi:10.1006/gyno.2000.5826.
11. Bray F, Carstensen B, Mallor H, et al. Incidence trends of adenocarcinoma of the cervix in 13 European countries. Cancer Epidemiol Biomarkers Prev 2005;14:2191-9. doi:10.1158/1055-9965.EPI-05-0231.
12. Nationellt Kvalitetsregister för Cervixcancerprevention. Förebyggande av livmoderhalscancer i Sverige. 2013. www.sfog.se/media/141284/nkcx__rrsrapport_2013_yt7.pdf
13. NKCx. Swedish National Cervical Screening Registry. Analysis. http://www.nkcx.se/index_e.htm
14. Swedish National Cervical Screening Registry. Förebyggande av livmoderhalscancer i Sverige. Verksamhetsberättelse och Årsrapport 2014 med data till och med 2013. http://ki.se/sites/default/files/arsrapport_2014.pdf
15. Statistics Sweden. http://www.scb.se/se_/.
16. World Health Organization. Statistical Code for Human Tumours (WHO/HS/CANC./24.1). World Health Organization, 1956.
17. Andreata B, Kermel L, Sparre P, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J Natl Cancer Inst 2008;100:622-9. doi:10.1093/jnci/djn099.
18. Sasioni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. Br J Cancer 2003;89:88-93. doi:10.1038/sj.bjc.6600974.
19. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, 2014. http://www.r-project.org/
Appendix 1: Supplementary tables A-E

Appendix 2: Supplementary figures A-B