Comparison of women with possible endocervical and non-cervical glandular neoplasms detected in liquid-based cervical cytology- incidence, clinical characteristics and outcomes: a cohort study

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Abstract

Objective:

To compare the incidence, demographics and clinical outcomes of women presenting with possible non-cervical (NC) and endocervical (EC) glandular neoplasms in their cervical smears.

Study Design:

Retrospective analysis of a prospective cohort within the NHS Greater Glasgow and Clyde- the largest health organisation in Scotland, UK.

Methods:

Cases identified from the Scottish Cervical Call Recall System between January 2013 and December 2017. Incidence and clinical trajectories of NC and EC were reviewed.

Results:

Two-hundred-and-thirty cases (NC=41; EC=189) from 486,240 smears were evaluated. The incidence was 8.4 and 38.9 per 100,000 smear-year for NC and EC, respectively.

Compared to women with EC, women with NC were significantly older ($p<0.0001$), had higher body mass index ($p<0.0001$), more likely to present with symptoms (58.5% vs 10.5%; $p<0.0001$), had cancers (48.8% vs 13.8%; $p<0.0001$) and died from their diseases (9.8% vs 0.5%; $p<0.0001$). Even in the asymptomatic screen-detected NC group, almost a quarter (23.5%) had endometrial cancer. Age was not associated with high-risk histology ($p=0.289$).

High-risk colposcopic appearance had good positive predictive value (90.0%; 95%CI: 81.2-95.6%) for high-risk histology, but poor negative predictive value (41.3%; 95%CI: 29-54%). Negative excision margin was associated with favourable outcomes.

Conclusions:

NC and EC are rare, but they are distinct and should be reported separately in future studies. The risks of malignancies are high, particularly in women with NC, even if they are asymptomatic. Thus, prompt and thorough investigations and treatments are required to prevent and treat malignancies.

Keywords: cervix, cervical smears, diagnosis, colposcopy, glandular neoplasms

1. Introduction

Glandular abnormalities are relatively uncommon in cervical cytology, compared to changes within the squamous epithelium.[1-4] Their incidence rates are thought to be increasing (the overall incidence was estimated to be 4.8 per 1000 smears performed in a population-based cohort study).[1, 5] The apparent increase has been attributed to improved sampling and processing techniques,[2, 3] increased recognition and refined definitions of glandular abnormalities and changes in the prevalence of human papillomavirus infection.[1]

The definitions of glandular abnormalities have undergone significant changes in recent years. In 2012, the third edition of Achievable Standards, Benchmarks for Reporting, and Criteria for Evaluating Cervical Cytopathology (ABC) recommended adoption of the revised British Society for Clinical Cytology (BSCC) terminology.[6] The revised terminology requires the differentiation between glandular neoplasia of non-cervical type (NC) and glandular neoplasia of endocervical type (EC), with EC encompassing both endocervical adenocarcinoma *in situ* and endocervical adenocarcinoma of the Bethesda system for cytology. The revised terminology was fully adopted by the National Health Service Cervical Screening Programme in the United Kingdom in 2013.[6]

Most existing studies reporting the care and outcomes of women with cervical glandular neoplasms were based on previous definitions without distinguishing between the EC and NC subtypes,[4, 5, 7-11] and the majority reported cases that were identified retrospectively when they presented to the specialists.[7, 8]

In this study, we utilised the prospectively collated Scottish Cervical Call Recall System (SCCRS) to identify possible glandular neoplasms detected by cervical cytology since the new terminology was adopted. The aim of this study was to review and compare the incidence, demographics, histological diagnoses and clinical outcomes of women presenting with possible glandular neoplasms on liquid-based cervical cytology based on the origin of their glandular changes.

2. Methods

2.1. Population and setting

SCCRS prospectively collates all cervical smear tests performed within Scotland. Each woman is linked with all her test results by her unique Community Health Index (CHI) number. This allowed the incidence of possible glandular neoplasms detected by cervical cytology to be calculated in this study.

The gynaecology services of the NHS Greater Glasgow and Clyde Health Board in West Central Scotland, the largest Scottish health board, are delivered by three different units with a shared digital clinical records system. All hospital clinical records have been digitalised since 2008.

2.2. Liquid-based cytology (LBC)

LBC was performed using the ThinPrep platform (Hologic, USA). In brief, each slide was imaged and 22 representative fields were reviewed by the first screener. All negative slides were rapid reviewed by another screener. All positive smears were screened in the conventional way by a trained cytology-screening technician and a clinician. No cell block was used for processing smears, and all women with smears suggestive of possible glandular neoplasms were referred to colposcopy or gynaecological assessment as per national guidance.

2.3. Cohort identification and review

Women with cervical cytology demonstrating possible NC and EC between January 2013 and December 2017 were identified by requesting a Business Objects Number 11 report via SCCRS. Clinical details and histopathology results were collected retrospectively by digital notes review. Deaths up to March 2020 were included in the analysis.

Any discrepancies between LBC results and histology of subsequent biopsies were further discussed and reviewed at the colposcopy multidisciplinary team meetings. H&E staining was routine for any excisional biopsy performed after identification of possible glandular neoplasms. Additional immunohistochemical staining may include p16 and bcl2 (the latter is performed when tubo-endometrioid metaplasia is a differential diagnosis). These are performed as determined by pathologists to aid definitive histological diagnosis. Final histological diagnoses reached were collated.

In this study, high-risk histology was defined as women diagnosed with malignancies, endometrial dysplasia, cervical glandular intraepithelial neoplasms (CGIN) and high-grade cervical intraepithelial neoplasms (CIN). High-risk colposcopic appearance was defined as documented changes consistent with high-grade cervical dysplasia or invasive cancers clinically identified during colposcopy.

2.4. Statistical analysis

Data were analysed using STATA® Version 16 (StataCorp, USA) and Figures were generated using GraphPad Prism 7 software. Time-trends were evaluated by linear regression. Categorical data were compared using chi-squared tests and non-parametric comparisons of continuous variables were performed using Mann-Whitney U test. A p-value of <0.05 was considered significant.

2.5. Ethical approval

This study systematically reviewed the care and outcomes of women with possible glandular neoplasms as an evaluation of an existing clinical service. Normal clinical management plans were not altered, and no patient identifiable detail was included. Therefore, formal ethical approval was not required.

Funding

No funding was received for the conduct of this study. All authors were employed by the NHS Greater Glasgow and Clyde Health Board (the salary of EL was also partially funded by the University of Glasgow).

3. Results

3.1. Incidence and demographics

Two-hundred-and-thirty women (NC=41; EC=189) with new possible glandular neoplasms were identified from 486,240 cervical smear tests performed between 2013-2017. The incidence rates of NC and EC were 8.4 and 38.9 per 100,000 smear-year, respectively (Figure 1). No significant increase in incidence was identified in both groups (R^2=0.580; p=0.135 and R^2=0.020; p=0.822 for NC and EC, respectively).

The demographics of women with NC and EC were summarised and compared in Table 1. Compared to women with EC, women with NC were significantly older (median 55 vs 34 years; p<0.0001), with higher body mass index (BMI; median 32.9 vs 24.8 kg/m^2; p<0.0001) and more likely to be symptomatic at first review (58.5% vs 10.5%; p<0.0001). No significant differences in smoking status, smear history, previous CIN and cervical treatment were identified. No smear was performed during pregnancy and the immediate post-partum period, as per national guidance in the UK.

3.2. Follow-up, assessments and investigations

The median follow-up was 4.5 years (interquartile range: 3.3-5.8). The initial assessments and investigations of women were summarised in Table S1, and relevant investigations are summarised schematically in Figure S1. Women were investigated in approximately 1 month from the time of their initial cervical smears, and most were reviewed at colposcopy clinics. One in 15 women (6.9%) with EC did not attend their initial assessments, despite additional appointments were offered.

Women with NC were primarily investigated by endometrial biopsies with transvaginal ultrasound and/or hysteroscopies, whilst women with EC were investigated by excisional biopsies (Table S1 and Figure S1). A large proportion of women were discussed at the regular multidisciplinary meetings (43.9% and 27.5% for NC and EC groups, respectively).

3.3. Histological diagnoses, management and mortality

Histological diagnoses and subsequent management were summarised in Table 2. High proportions of women in both groups had high risk histology (58.6% and 71.5% for NC and EC groups, respectively). Women with NC were significantly more likely to have

gynaecological malignancies at presentation (48.8% vs 13.8%; p<0.0001) and hysterectomy or debulking surgeries (46.3% vs 22.2%; p=0.002), compared to women with EC. One woman with previous breast cancer presented with post-menopausal bleeding and was investigated by hysteroscopy, cervical cytology and ultrasound scan, subsequent biopsies confirmed metastatic high-grade serous ovarian cancer. Women with NC were also more likely to die from cancer (9.8% vs 0.5%; p<0.0001), compared to women with EC. The only death in the EC group was from lung carcinoma.

3.4. The relationships between symptoms and histological diagnosis in women with NC

As most women in the NC group had symptoms at initial presentation and were at high risk of malignancies, the relationships between the presence of symptoms and histological diagnoses were also evaluated to clarify the risk of malignancies in the asymptomatic, i.e. screen-detected, NC subgroup (Table 3). Asymptomatic women were less likely to have malignancies than symptomatic women in the NC group (23.5% vs 58.3%; p=0.027). However, even in this asymptomatic group, women with NC were more likely to have malignancies than women in EC group (13.8%; Table 2).

3.5. The relationships between colposcopy findings and histological diagnosis

The relationships in women with recorded colposcopic findings and histological diagnoses were summarised in Table 4. The accuracy of high-risk colposcopic appearance to predict high-risk histological diagnoses (as defined in methods) was evaluated. The sensitivity and specificity of high-risk colposcopic appearance to identify high-risk histological diagnoses were 66.1% (95%CI: 56.4-74.9%) and 76.5% (95%CI: 58.5-89.3%), respectively.

The false positive and false negative rates of high-risk colposcopic appearance to identify women with high-risk histological diagnoses were 5.6% and 25.9%, respectively. The positive predictive value and negative predictive value of high-risk colposcopic appearance to predict high-risk histological diagnoses were 90.0% (95%CI: 81.2-95.6%) and 41.3% (95%CI: 29-54%), respectively.

3.6. The relationships between age and histological diagnosis

The relationships between age and histological diagnosis in the EC group was summarised in Table S2a. No significant difference in high-risk or low-risk histology was identified in this group. In the NC group, only 1 woman were less than 35 years old, who had no abnormality detected after thorough investigations. However, in women over 50 years old, NC glandular smears were more likely to have high-risk histology (20%vs 71%, p=0.004; Table S2b).

3.7. The relationships between biopsy margins and outcomes

Data from 146 women who have undergone excisional biopsies and with no malignancy identified in their initial histological specimens were summarised in Table S3. Women with negative margins in their excisional biopsies were more likely to have normal cytology at 6 months (67.4%) and less likely to have second excisional procedures (9.0%) and hysterectomies (3.4%), compared to women with positive or undetermined margins (Table S3). The majority of women with negative margins in their excisional biopsies had further treatment due to subsequent borderline or dissatisfactory cervical cytology results.

4. Discussion

Glandular neoplasms in cervical smears are rare (~5 per 10,000 smear-year), with EC almost 5 times more than NC. While few studies based on the BSCC terminology have reported the incidence of glandular neoplasms cytology, two recent studies based on the Bethesda system from the US and Sweden have reported low incidence of cervical cytology with atypical glandular cells, which also included atypical glandular cells not otherwise specified (AGC-NOS; 0.5-0.6% of all women screened).[4, 5] This is a large and one of the most comprehensive cohort studies of this rare cervical cytology category, evaluating and comparing the demographics, histological diagnoses, management and outcomes of women with possible NC and EC.

In addition, utilising a prospective population-based database (SCCRS), we were able to estimate the incidence of NC and EC. A significant increase in the incidence of cervical glandular neoplasms was not observed during the study period (Figure 1). This supported the suggestion that part of the observed increased incidence rate reported in the literature could be attributed to processing and interpretation of cervical glandular abnormalities.[1]

This study also confirmed the distinct demographics, histopathology diagnoses and management between the NC and EC group (Table 1-3, Table S1). In particular, women with NC were older and the majority were obese. They were also more likely to present with symptoms, had cancers and died from their diseases.

Women presented with possible NC were at particularly high risk of malignancies (Table 3). Even in the screen-detected asymptomatic NC group, almost a quarter (23.5%) had endometrial cancer- twice as likely than women presented with post-menopausal bleeding (9-10%).[12]

With comprehensive review of the digitalised medical records, we evaluated the accuracy of colposcopy findings in this cohort (Table 4). While high-grade/invasive colposcopic findings had good positive predictive value (90.0%; 95%CI 81.2-95.6%), their negative predictive value (41.3%; 95%CI 29-54%) was less robust, with a relatively high false negative rate (25.9%).

Age (<35 years old) has previously been suggested as a risk stratification strategy for women with cervical glandular abnormalities.[2, 7] However, our results did not demonstrate a significant difference in histological diagnoses between the two age groups using this cut-off (Table S2a). It is possible that the metaplastic or hyperplastic changes in the cervix during puberty, pregnancy and exposure to exogenous oestrogen (e.g. the oral contraceptive pills) in younger women are associated with borderline glandular changes, but not the high-risk glandular neoplastic changes evaluated in this study. Consistent with previous data,[13] older women ($\geq$50 years old) presented with non-cervical glandular smears were more likely to have high-risk histological diagnoses (Table S2b). Future studies should further clarify the use of age cut-offs to stratify the management of glandular abnormalities in cervical cytology.

Excision margin is an established prognostic indicator for women undergoing excisional biopsies.[14, 15] Consistent with previous reports,[14, 15] negative excision margins conferred good outcomes- two-thirds of women had normal smears at 6 months, and only 1

in 10 and 1 in 30 required further excisional biopsies and hysterectomies, respectively (Table S3).

Although this study reviewed almost half a million smears over a 5-year period, the outcomes and practice may not be generalisable to other populations outside the United Kingdom. Moreover, a single team of histopathologists and cytologists with automated and standardised cytology processing capabilities have processed these smears to maximise reproducibility. Prior research demonstrated only moderate inter-observer variations of the diagnosis of glandular lesions[16]- our results may not be representative of centres that process fewer cervical cytology samples. In addition, the smears were classified based on the BSCC terminology, which cannot be easily translated into the Bethesda system for reporting cervical cytology used elsewhere in the world. The longer follow-up for those who did not undergo hysterectomies is also warranted as a prior population-based cohort study has demonstrated persistently elevated risks of cervical adenocarcinoma for up to 15 years after the first identification of atypical glandular smears (based on the Bethesda system).[5]

Primary HPV screening had yet to be introduced during the study period, so we could not evaluate the role of HPV testing on the management of EC and NC. Although HPV has been suggested as a helpful triage tool for the glandular abnormalities in cervical cytology, HPV negative glandular abnormalities will not be identified by primary HPV-testing-only screening strategy. In a recent population-based cohort study,[11] approximately 43.6% of atypical glandular cells detected in cervical cytology were HPV-negative. In this group, 10/170 (5.9%) had high-risk histology (5 cervical high-grade lesion and 5 endometrial cancers). A recent meta-analysis demonstrated 19.3% of women who were less than 40 years old presented with HPV-negative glandular abnormalities had CIN2/CIN3, CGIN or cervical cancer.[10] The potential of missing this small but clinically significant group of women with glandular neoplasms should be taken into account when comparing the cost-effectiveness of different cervical screening strategies.

5. Conclusions

The risks of malignancies are high in women with cytology suggestive of NC and EC, particularly in women with NC, even if they are asymptomatic. Thus, prompt and thorough treatments and investigations are required to prevent and treat malignancies after receiving these rare cervical cytology results.

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Contribution to authorship:

EYLL, ML, RG contributed to conceptualization and methodology. RM, HY, EYLL contributed to data curation. EYLL performed formal analysis and visualisation and the original draft of this manuscript. The manuscript was then reviewed, edited and approved by all authors.

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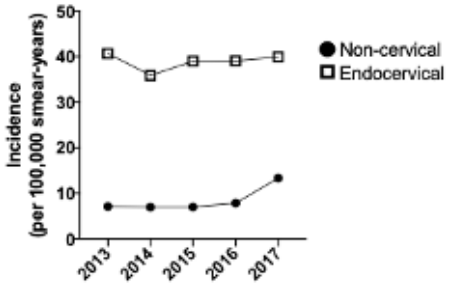
InterpretationsRealistic Estimates From the ASCUS-LSIL Triage Study. JAMA. 2001;285(11):1500-5.

Figure 1: Incidence of cervical cytology suggestive of glandular neoplasms over time (per 100,000 smear-years)



	2013	2014	2015	2016	2017	Overall
Non-cervical	7.1	7.0	7.0	7.8	13.3	8.4
Endocervical	40.7	35.9	39.0	39.0	39.9	38.9

Table 1: Demographics of women with cervical cytology suggestive of glandular neoplasms (n=230)

		Non-cervical (n=41)	**Endocervical** (n=189)	**p-value**
Age (years)		55 (51-58)	34 (30-42)	<0.0001
BMI (kg/m^2)		32.9 (28.7-39.9)	24.8 (22.3-30.1)	<0.0001
Smear history	Up-to-date	21 (51.2%)	119 (63.0%)	0.259
	Overdue	14 (34.1%)	55 (29.1%)	
	Never	6 (14.6%)	15 (7.9%)	
Previous CIN	Total	3 (7.3%)	17 (9.1 %)	0.716
	Low grade	0 (0%)	8 (4.2%)	
	High grade	3 (7.3%)	9 (4.8%)	
Previous Treatments	Total	2 (4.9%)	14 (7.4%)	0.564
	LLETZ	2 (4.9%)	12 (6.3%)	
	Cone biopsy	0 (0%)	1 (0.5%)	
	CC	0 (0%)	1 (0.5%)	
Smoking status	Never	31 (75.6%)	108 (57.1%)	0.114
	Ex-smoker	6 (14.6%)	20 (10.6%)	
	Smoker	4 (9.8%)	42 (22.2%)	
	Not recorded	0 (0%)	19 (10.1%)	
Symptomatic	No	17 (41.5%)	149 (78.8%)	<0.0001
	Yes	24 (58.5%)	20 (10.5%)	
	Not recorded	0 (0%)	20 (10.5%)	

Median (interquartile range) for age; LLETZ: large loop excision of transformation zone; CC: cold coagulation; BMI: body mass index (recorded in 36 [87.8%] for NC and 138 [73.0%] for EC); CIN: cervical intraepithelial neoplasm.

Table 2: Histological diagnoses and subsequent management of women with cervical cytology suggestive of glandular neoplasms (n=230)

		Non-cervical (n=41)	**Endocervical** (n=189)	**p-value**
Histological diagnosis	Gynaecological cancers	20 (48.8%)	26 (13.8 %)	<0.0001
	• Cervical	• 0 (0%)	• 26 (13.8%)	
	• Endometrial	• 18 (43.9%)	• 0 (0%)	
	• Ovarian	• 2 (4.9%)	• 0 (0%)	
	Other high-risk histology	4 (9.8%)	109 (57.7%)	<0.0001
	• Endometrial	• 3 (7.3%)	• 0 (0%)	
	• CGIN	• 0 (0%)	• 74 (39.2%)	
	• High-grade CIN	• 1 (2.4%)	• 35 (18.5%)	
	Low-risk histology	17 (41.5%)	44 (23.3%)	0.017
	• Low-grade CIN	• 0 (0%)	• 3 (1.6%)	
	• Other benign	• 3 (7.3%)	• 21 (11.1%)	
	• Normal	• 14 (34.1%)	• 20 (10.6%)	
	Inadequate	0 (0%)	2 (1.1%)	
	Not recorded	0 (0%)	7 (3.7%)	
	Not indicated	0 (0%)	1 (0.6%)	
Management	Hysterectomy/ debulking	19 (46.3%)	42 (22.2%)	0.002
	LLETZ	3 (7.3%)	169 (89.4%)	<0.0001
	Chemotherapy/ radiotherapy	3 (7.5%)	3 (1.6%)	
	Levonorgestrel IUS	4 (9.8%)	0 (0%)	
	Not indicated*	14 (34.1%)	10 (5.3%)	
Cancer-related death		4 (9.8%)	1 (0.5%)	<0.0001

*Histological diagnosis not indicated in 1 case after cytology review demonstrating reactive changes only; IUS: intrauterine system; CIN: cervical intraepithelial neoplasm; CGIN: cervical glandular intraepithelial neoplasm.

Table 3: The relationships between symptoms at presentation and histological diagnosis in women with cervical cytology suggestive of NC (n=41)

Symptoms	Present (n=24)	Absent (n=17)	p-value
Endometrial cancer	14 (58.3%)	4 (23.5%)	0.027
Ovarian cancer	1 (4.2%)	1(5.9%)	1.000
Hyperplasia/Dysplasia	3 (12.5%)	1 (5.9%)	0.482
Other benign	2 (8.3%)	1 (5.9%)	0.767
Normal	4 (16.7%)	10 (58.8%)	0.005

Table 4: The relationships between colposcopic findings and histological diagnosis in women with cervical cytology suggestive of EC (n=143)

	High-risk histology			**Low-risk histology**		
	Cancer (n=22)	**CGIN** (n=60)	**HG CIN** (n=27)	**LG CIN** (n=2)	**Benign** (n=17)	**Normal** (n=15)
Invasion	6 (27.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
High grade	10 (45.5%)	35 (58.3%)	21 (77.8%)	1 (50%)	3 (17.6%)	4 (26.7%)
Low grade	2 (9.1%)	8 (13.3%)	2 (7.4%)	1 (50%)	4 (23.5%)	2 (13.3%)
Benign*	2 (9.1%)	4 (6.7%)	0 (0%)	0 (0%)	1 (5.9%)	2 (13.3%)
Normal	2 (9.1%)	13 (21.7%)	4 (14.8%)	0 (0%)	9 (52.9%)	7 (46.7%)

*HPV-related changes, inflammatory changes and other benign changes; HG: high-grade; LG: low-grade; CIN: cervical intraepithelial neoplasm; CGIN: cervical glandular intraepithelial neoplasm.