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Atypical glandular lesions of the cervix and risk of cervical cancer

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Abstract

Introduction: Cytology screening has been effective in reducing risks for cervical squamous cell carcinoma but less so for adenocarcinoma. We explored the association of atypical glandular cells or absence of glandular cells in cytology, and subsequent histological diagnoses and cancer risk.

Material and methods: All women in Norway with atypical glandular cells of undetermined significance (AGUS), adenocarcinoma in situ (ACIS) and normal/benign cells, but absence of endocervical or metaplastic cells (NC-NEC) in their first cytology during 1992-2014 (NC-NEC; 2005-2014), recorded in the Cancer Registry of Norway, were included (n = 142 445). Histology diagnoses (stratified by age) within 1 and 3 years after cytology were examined. The Nelson-Aalen cumulative hazard function for gynecological cancer risk was displayed.

Results: The majority of AGUS and particularly ACIS were followed with histology within 1 and 3 years. Cervical intraepithelial neoplasia (CIN) lesions were more common in women <35 than in women ≥35 years. Cervical adenocarcinoma followed 13% of ACIS after 1 and 3 years. After ACIS and AGUS, cervical adenocarcinoma was the most frequent cancer subtype. Cumulative risks of cervical adenocarcinoma following ACIS, AGUS and NC-NEC were 3.5%, 0.9% and 0.05%, respectively, after 22, 22 and 9 years of follow up.

Conclusions: There was a high-risk of glandular malignancies after AGUS and ACIS in cytology. If effective treatment of pre-cancer and early cancer is available, cytology screening provides some level of prevention of adenocarcinoma. Lack of glandular cells did not entail a higher cancer risk.

KEYWORDS

atypical glandular lesions, cervical cancer, cytology

Abbreviations: ACIS, adenocarcinoma in situ; AEC, atypical endocervical cells; AGC, atypical glandular cells; AGUS, atypical glandular cells of undetermined significance; CIN, cervical intraepithelial neoplasia; CRN, Cancer Registry of Norway; HPV, human papillomavirus; ICD-7, International Classification of Diseases, 7th revision; NCCSP, Norwegian Cervical Cancer Screening Program; NC-NEC, normal/benign cells, but absence of endocervical or metaplastic cells.

1 | INTRODUCTION

Cervical cancer is the fourth most common cancer among women worldwide, with around 570 000 new cases and 310 000 deaths in 2018.[1] Well-organized cervical cancer screening programs have produced profound decreases in incidence and mortality of the disease.[2,3] In Norway, a decline in cervical cancer incidence and mortality was seen after the implementation of organized screening in 1995, but incidence rates seem to have increased during recent years.[3]

The Norwegian Cervical Cancer Screening Program (NCCSP) invites all women aged 25-69 years to screening with cytological smears every 3 years.[4] The screening coverage in the target age group is 69% within 3.5 years (2013-2016).[3] Low-grade squamous cell cytological abnormalities are triaged with human papillomavirus (HPV) testing and intensified screening, whereas high-grade cytological abnormalities warrant immediate referral to colposcopy and biopsy.[5] Randomized implementation of HPV primary screening started in four Norwegian counties in 2015,[6] and will be gradually implemented in the remaining counties during 2019-2021.

In some settings, cervical screening using cytology has been reported to reduce the risk of invasive adenocarcinomas,[7,8] and lead to earlier detection of this type of cancer.[9] However, cytology has been much more successful in reducing the risk of developing squamous cell carcinoma.[2,8,10] Consequently, the relative contribution of these two main histological subtypes to the total cervical cancer burden has been changing over decades in countries with effective screening programs.[11]

The proportions of cytological smears that display dysplasia and/or abnormalities vary considerably between countries (0.98%-15.5%).[12-16] Histological diagnosis of adenocarcinoma in situ (ACIS) can follow either glandular or squamous cytological abnormalities. In American material, about 3%-4% of women with abnormal cytology have ACIS in histology.[17,18]

Of all cervical smears, 0.1%-2.1% are classified as atypical glandular cells of undetermined significance (AGUS).[17,19,20] A significant proportion of women with such smears have underlying cancer, or will develop cancer during follow up.[20] Among women with AGUS in cytology in a US primary-care study, 19.5% had cancerous squamous or glandular lesions of the cervix or endometrium and 11.5% had pre-cancerous squamous or glandular lesions.[21] In a Swedish cohort study, women with atypical glandular cells (AGC), equivalent to AGUS, in cervical screening had a higher risk of incident cervical carcinoma, especially adenocarcinoma, than women with a high-grade squamous intraepithelial lesion.[22] The cumulative incidence of invasive cervical cancer was persistently elevated for up to 15.5 years following AGC in cytology.

Smears labelled as normal/benign cells, but with absence of endocervical or metaplastic cells (NC-NEC) in our study show normal cells, but lack endocervical or metaplastic cells. As such, the condition of endocervical or metaplastic cells cannot be evaluated in these samples. NC-NEC smears are managed as normal smears in NCCSP.[5] A Canadian review from 2011 suggested that the absence of endocervical cells in smears does not indicate a higher risk for underlying cervical abnormalities,[23] but little is known in the Norwegian setting.

Key message

There is a high risk of cervical adenocarcinoma after atypical glandular cells in cytology. Absence of glandular cells in cytology did not entail a higher cervical cancer risk.

This study aimed to describe the association between atypical glandular changes in cervical cytology; AGUS, ACIS and NC-NEC, and subsequent diagnoses verified by histology. We also examined the risk of developing cervical cancer by histological subtype and other gynecological malignancies over time.

2 | MATERIAL AND METHODS

2.1 | Data sources

Data from the Cancer Registry of Norway (CRN), including NCCSP, were used.

The CRN was established in 1953 and covers the entire population. The registry contains information on all new cancer cases and certain pre-cancerous lesions. Site, histological type and stage of disease at the time of diagnosis are reported, and clinical notifications, pathological notifications and death certificates are the main reporting sources. The coding and classification systems at CRN follow international standards. Reporting of cancer cases is compulsory in Norway, and the data have been evaluated to be accurate and close to complete.[24]

The NCCSP is an integrated part of the Norwegian national healthcare system, and is managed by the CRN. The program receives mandatory reports from public and private pathology and microbiology laboratories, and keeps complete records of cytology, histology and HPV test results. Individual screening data are recorded and organized into four sub-registries; the Cytology Register (since 1991), the Histology Register (since 2002), the HPV Test Register (since 2005) and the cervical intraepithelial neoplasia (CIN) Register (since 1997).[25] The CIN Register also includes follow-up and treatment data. The Bethesda and the SNOMED coding systems, with some local adaptions and changes over time, have been used for classification (cytology and histology).[26]

2.2 | Study population

This study included all women in Norway with AGC in their first registered cervical cytology (AGUS and ACIS) since 1992, and all women with NC-NEC in their first cervical cytology since 2005 (when this category was adopted) (n = 142 445) (Figure 1). We

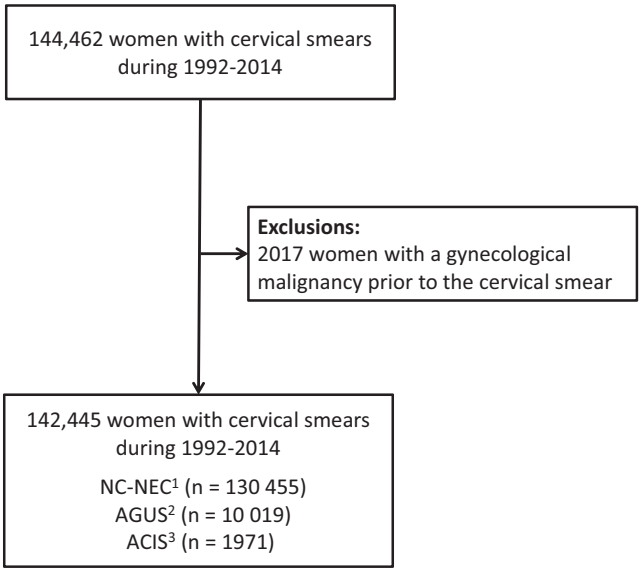

FIGURE 1 Selection of the study population; all women in Norway diagnosed with atypical glandular changes and normal/benign cells, but absence of endocervical or metaplastic cells, in their first cervical cytology during 1992-2014. [1]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005. [2]Atypical glandular cells of undetermined significance. [3]Adenocarcinoma in situ [Color figure can be viewed at wileyonlinelibrary.com]

excluded women who had a diagnosis of invasive cervical cancer or other gynecological malignancies before their first cytology (n = 2017).

2.3 | Statistical analyses

Histology diagnoses recorded within 1 and 3 years after cervical cytology during 2002-2014 for AGUS and ACIS and during 2005-2014 for NC-NEC, and stratified by age (<35 and ≥35 years), were descriptively displayed using contingency tables. No information on histology was available before 2002. Due to small numbers, no statistical tests examining differences between groups were performed.

The Nelson-Aalen cumulative hazard function for risk of gynecological cancers, with 95% CIs, was calculated.[27] We identified all gynecological cancers, cervical cancer (International Classification of Diseases 7th revision [ICD-7]; 171), uterine corpus cancer (ICD-7; 172), ovarian cancer (ICD-7; 175.0) and vulvar/vaginal cancers (ICD-7; 176). The two main histological sub-groups of cervical cancer (squamous cell carcinoma and adenocarcinoma) were considered separately. Follow up started at 3 months after the cervical smear to exclude prevalent cancers detected at the index screen, and ended at diagnosis of a gynecological cancer, emigration, death or 31 December 2013, whichever occurred first.

The data were analyzed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) and Stata/IC 14.0 (StataCorp., College Station, TX, USA).

2.4 | Ethical approval

The Regional Committee for Medical and Health Research Ethics of Western Norway approved the study (REK ref. number 2014/1918).

3 | RESULTS

3.1 | Characteristics of the study population

The median ages at ACIS, AGUS and NC-NEC were 43, 44 and 45 years, respectively. Within 1 and 3 years of cytology, respectively, 91% and 92% of ACIS, 76% and 78% of AGUS, and 2% and 3% of NC-NEC smears were followed by a histological diagnosis (2002-2014).

3.2 | Association between cytological smears and histological diagnoses

Dysplastic lesions, premalignant lesions and cervical malignancies such as adenocarcinomas and squamous cell carcinomas were more frequent after ACIS cytology, and there were no major differences after 1 year (74.3%) and 3 years of cytology (75.4%). Following AGUS and ACIS cytology, 55.6% and 20.2% of the histological diagnoses within 3 years were normal or benign, respectively. CIN3 accounted for the majority of the CIN lesions following both AGUS and ACIS, whereas CIN1/2 were more frequent following AGUS cytology than ACIS after both 1 and 3 years. Overall, CIN1-3 accounted for 26.7% and 28.6% of the histological diagnoses within 1 and 3 years of AGUS, and 27.3% and 26.6% within 1 and 3 years of ACIS cytology (Tables 1 and 2). Following AGUS cytology, 38.7% and 41.7% of the histological diagnoses were dysplastic, premalignant and malignant (about 25% were CIN3, ACIS or more severe within 1 and 3 years). The majority of the histological diagnoses following NC-NEC within 1 (81.1%) and 3 years (77.4%) were normal or benign. CIN1-3 accounted for 12.0% and 15.9% of the histological diagnoses within 1 and 3 years, respectively (Tables 1 and 2).

3.3 | Association between cytological smears and histological diagnoses, stratified by age

Following ACIS cytology, the proportion of CIN1 and CIN2 histology was similar in women aged <35 and ≥35 years (Tables 3 and 4). ACIS was the most common histology diagnosis in both age groups. Malignant lesions had a higher proportion in women ≥35 than in women <35 years following ACIS cytology. There was a larger proportion of CIN lesions overall in women <35 than in women ≥35 years following AGUS cytology. Histology diagnosis of invasive adenocarcinoma was more common in women ≥35 years, whereas the proportion of squamous cell carcinoma following AGUS cytology was similar in women <35 and ≥35 years (Tables 3 and 4). Normal

TABLE 1 Distribution of histology diagnoses recorded within 1 year of cervical cytology, Norway, 2002/05-2014

Histology	Cytology					
	NC-NEC[a]		AGUS[b]		ACIS[c]	
	n	%	n	%	n	%
Normal/benign	1702	81.1	2362	58.4	134	20.9
Insufficient or unsatisfactory material for diagnosis	112	5.3	92	2.3	11	1.7
Most likely malignant	3	0.1	60	1.5	4	0.6
CIN1	101	4.8	294	7.3	16	2.5
CIN2	45	2.1	169	4.2	18	2.8
CIN3	105	5.0	617	15.3	141	22.0
Irregular glandular epithelium	4	0.2	73	1.8	14	2.2
ACIS	3	0.1	203	5.0	183	28.6
Cervical cancer						
Squamous cell carcinoma	11	0.5	41	1.0	11	1.7
Adenocarcinoma	1	0.0	102	2.5	84	13.1
Unspecified or other	1	0.0	6	0.1	5	0.8
Metastasis	11	0.5	26	0.6	19	3.0
Total	2099	100	4045	100	640	100

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005.

[b]Atypical glandular cells of undetermined significance.

[c]Adenocarcinoma in situ.

TABLE 2 Distribution of histology diagnoses recorded within 3 years of cervical cytology, Norway, 2002/05-2014

Histology	Cytology					
	NC-NEC[a]		AGUS[b]		ACIS[c]	
	n	%	n	%	n	%
Normal/benign	2903	77.4	2513	55.6	147	20.2
Insufficient or unsatisfactory material for diagnosis	176	4.7	93	2.1	11	1.5
Most likely malignant	11	0.3	67	1.5	6	0.8
CIN1	198	5.3	349	7.7	19	2.6
CIN2	106	2.8	202	4.5	21	2.9
CIN3	291	7.8	742	16.4	154	21.2
Irregular glandular epithelium	6	0.2	84	1.9	18	2.4
ACIS	13	0.3	268	5.9	220	30.2
Cervical cancer						
Squamous cell carcinoma	23	0.6	51	1.1	12	1.6
Adenocarcinoma	5	0.1	113	2.5	94	12.9
Unspecified or other	3	0.1	7	0.2	6	0.8
Metastasis	16	0.4	31	0.7	29	4.0
Total	3751	100	4520	100	728	100

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005.

[b]Atypical glandular cells of undetermined significance.

[c]Adenocarcinoma in situ.

and benign was the most common histology after NC-NEC in both women <35 years (over 50% within 1 and 3 years) and ≥35 years (over 80% within 1 and 3 years) (Tables 3 and 4). There were few histological diagnoses of ACIS following NC-NEC cytology within 3 years in women <35 (0.8%) and ≥35 (0.2%) years (Table 4). Malignant lesions (squamous cell carcinoma and adenocarcinoma) were rare in both age groups.

3.4 | Cumulative risk of gynecological cancer according to cervical cytology

A total of 121 023 women were followed from 3 months after the cervical smear (Table 5). For ACIS, AGUS and NC-NEC the mean follow-up times were 12.6, 10.3 and 4.6 years, respectively. Of the women with ACIS, AGUS and NC-NEC in cytology, 6.5%, 2.6% and 0.3% developed gynecological cancer. For ACIS and AGUS, cervical cancer was the most common gynecological cancer and adenocarcinoma was the most frequent histological subtype. The cumulative risk of all gynecological cancers increased steeply in women with ACIS during the first 2 years, and continued to increase during follow up (Figure 2). The cumulative risks were lower for AGUS. The cumulative risks of all gynecological cancers following ACIS, AGUS and NC-NEC were 8.1%, 5.5% and 0.9% after 22, 22 and 9 years of follow up, respectively. For cervical adenocarcinoma, the cumulative risks were 3.5%, 0.9% and 0.05%.

4 | DISCUSSION

In this nationwide population-based cohort study, we described the association between atypical glandular changes in cervical cytology and subsequent diagnoses verified by histology. We also examined the risk of developing cervical cancer and other gynecological malignancies over time. Women <35 years old were more likely to have premalignant lesions (CIN1/2/3 and ACIS) after verified AGUS or ACIS cytology. There were no major differences 1 and 3 years after ACIS cytology, where 74.3% and 75.4% had developed dysplastic lesions, premalignant lesions and cervical malignancies. The figures after AGUS cytology were 38.7% and 41.7%, respectively.

TABLE 3 Distribution of histology diagnoses recorded within 1 year of cervical cytology, Norway, 2002/05-2014, in women <35 and ≥35 years of age

	Cytology											
	NC-NEC[a]				AGUS[b]				ACIS[c]			
	<35 y		≥35 y		<35 y		≥35 y		<35 y		≥35 y	
Histology	n	%	n	%	n	%	n	%	n	%	n	%
Total	336	100.0	1763	100.0	848	100.0	3197	100.0	165	100.0	475	100.0
Normal/benign	198	58.9	1504	85.3	329	38.8	2033	63.6	23	13.9	111	23.4
Insufficient or unsatisfactory material for diagnosis	4	1.2	108	6.1	10	1.2	82	2.6	1	0.6	10	2.1
Most likely malignant	0	0	3	0.2	5	0.6	55	1.7	0	0	4	0.8
CIN1	52	15.5	49	2.8	69	8.1	225	7.0	6	3.6	10	2.1
CIN2	18	5.4	27	1.5	64	7.5	105	3.3	4	2.4	14	2.9
CIN3	59	17.6	46	2.6	235	27.7	382	11.9	41	24.8	100	21.1
Irregular glandular epithelium	0	0.0	4	0.2	21	2.5	52	1.6	6	3.6	8	1.7
ACIS	1	0.3	2	0.1	90	10.6	113	3.5	65	39.4	118	24.8
Cervical cancer												
Squamous cell carcinoma	4	1.2	7	0.4	9	1.1	32	1.0	1	0.6	10	2.1
Adenocarcinoma	0	0	1	0.1	16	1.9	86	2.7	17	10.3	67	14.1
Unspecified or other	0	0	1	0.1	0	0	6	0.2	1	0.6	4	0.8
Metastasis	0	0	11	0.6	0	0	26	0.8	0	0	19	4.0

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005.

[b]Atypical glandular cells of undetermined significance.

[c]Adenocarcinoma in situ.

After ACIS, 66.3% and 66.8% developed CIN3+ after 1 and 3 years, whereas the figures were 24.0% and 26.1% after AGUS. The high risk of high-grade lesions after AGUS justifies the immediate diagnostic verification and follow up of this lesion. Gynecological cancer most frequently followed ACIS cytology, and cervical adenocarcinoma was the most common histological subtype. Normal and benign was the most common histology after NC-NEC, and malignant lesions were rare.

More than half of the histological diagnoses following AGUS smears were normal or benign, and more common in women >35 years of age in our study. This is in line with a review where 11 of 19 included studies reported a predominance of benign or normal histology following AGUS/AGC, but where normal and benign findings varied from 20% to 80% in the different studies.[20]

Still, a significant proportion of women with AGUS have or will develop high-grade histological lesions and some may also develop gynecological cancer. In our study, about a quarter of the women with AGUS were diagnosed with high-grade histological lesions within 1 year. These might be considered underlying lesions detected by cytology screening. A 2016 meta-analysis of 12 studies on high-risk HPV testing in the management of AGC, indicated that 20% of women with AGC developed CIN2+/ACIS+ when followed up by the screening program in the respective countries.[28] In total, about 5% of women with AGC cytology in that analysis had ACIS+ histology. Cervical malignancies (squamous cell carcinoma, adenocarcinoma and adenosquamous carcinoma) were detected in 3.6%.

Marques et al[20] did a systematic review of 19 articles that addressed the correlation of AGUS/AGC in cytology and benign, premalignant and malignant lesions. Premalignant squamous lesions were predominant in 6 of the articles whereas cervical adenocarcinoma and endometrial adenocarcinoma had proportion ranges of 0%-18%[29,30] and 0%-29%,[29,31] respectively. Another relatively recent Australian study (2015) found that 11.8% of women with atypical endocervical cells (AEC) cytology had or developed an ACIS or CIN2/3 histology diagnosis within 5 years, and 0.7% and 3.8% of women were diagnosed with cervical and endometrial carcinomas, respectively.[32]

Previous research has found that women aged 24-35 years with AEC more likely have high-grade cervical dysplasia than older women, especially during the first 3-4 years following the AEC smear.[32] Our findings also indicated a higher proportion of high-grade cervical dysplasia among women <35 years of age within 1 and 3 years after AGUS cytology. Because sexual intercourse with new partners remains a risk factor for HPV infection and the rates of acquiring new partners decline with age, these findings may be correlated to the natural course of HPV infections in younger women. According to Schiffman et al,[33] the majority of newly acquired HPV infections become undetectable within 1-2 years. However, HPV infections persistently detected beyond 12 months increase the

TABLE 4 Distribution of histology diagnoses recorded within 3 years of cervical cytology, Norway, 2002/05-2014, in women <35 and ≥35 years of age

	Cytology											
	NC-NEC[a]				AGUS[b]				ACIS[c]			
	<35 y		≥35 y		<35 y		≥35 y		<35 y		≥35 y	
Histology	n	%	n	%	n	%	n	%	n	%	n	%
Total	726	100.0	3025	100.0	985	100.0	3535	100.0	196	100.0	532	100.0
Normal/benign	373	51.4	2530	83.6	357	36.2	2156	61.0	26	13.3	121	22.7
Insufficient or unsatisfactory material for diagnosis	11	1.5	165	5.5	10	1.0	83	2.3	1	0.5	10	1.9
Most likely malignant	1	0.1	10	0.3	5	0.5	62	1.8	0	0	6	1.1
CIN1	101	13.9	97	3.2	80	8.1	269	7.6	7	3.6	12	2.3
CIN2	53	7.3	53	1.8	70	7.1	132	3.7	5	2.6	16	3.0
CIN3	174	24.0	117	3.9	285	28.9	457	12.9	44	22.4	110	20.7
Irregular glandular epithelium	1	0.1	5	0.2	21	2.5	59	1.7	8	4.1	10	1.9
ACIS	6	0.8	7	0.2	121	12.3	147	4.2	82	41.8	138	25.9
Cervical cancer												
Squamous cell carcinoma	5	0.7	18	0.6	14	1.4	37	1.0	1	0.5	11	2.1
Adenocarcinoma	1	0.1	4	0.1	18	1.8	95	2.7	21	10.7	73	13.7
Unspecified or other	0	0	3	0.1	0	0	7	0.2	1	0.5	5	0.9
Metastasis	0	0	16	0.5	0	0	31	0.9	0	0	20	3.8

Abbreviation: CIN, cervical intraepithelial neoplasia.

[a]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005.

[b]Atypical glandular cells of undetermined significance.

[c]Adenocarcinoma in situ.

risk of carcinogenic progression to cervical pre-cancer or cancer if untreated.

In our study, 2.6% of women with AGUS developed gynecological cancer and 1.3% developed cervical cancer after a mean follow up of 10.3 years. A Swedish cohort study by Wang et al[22] assessed the short-term and long-term risks of cervical cancer after AGC cytology with a mean follow up of 10 years, and found a prevalence of cervical cancer of 1.4%.

Cervical cancer and uterine corpus cancer were the most common gynecological cancers following AGUS cytology in our study. Adenocarcinoma constituted more than half of the cervical cancer cases following AGUS cytology, whereas about 40% were squamous cell carcinoma. Wang et al[22] found that the most prevalent cervical cancers were diagnosed within 6 months after AGC, and the highest incidence and prevalence of cervical cancer were found in women aged 30-39 years. Adenocarcinoma was the main histological subtype of cervical cancer (73.2%), whereas squamous cell carcinoma accounted for 22.1%. This would imply an even higher specificity of AGC for carcinomas of the glandular subtype than found in our material for AGUS cytology. Together, these findings indicate that a considerable cancer risk is associated with AGUS cytology.

Munro et al[32] found that 4.8% of women with AEC had invasive malignancies. Endometrial cancer was most frequent, especially in women >45 years of age. Geier et al[18] found only 0.2% endometrial adenocarcinomas (1 case within 1 year of follow up), whereas the

TABLE 5 Gynecological malignancies following cervical cytology, 1992-2013

	Cytology		
Characteristics	NC-NEC[a]	AGUS[b]	ACIS[c]
Mean follow up (y)[d]	4.6	10.3	12.6
Number and proportion (%) of malignancies following cytology			
Cervical cancer[e] (ICD-7; 171)	55 (0.0)	116 (1.3)	65 (4.2)
Adenocarcinoma	12 (0.0)	61 (0.7)	45 (2.9)
Squamous cell carcinoma	41 (0.0)	46 (0.5)	14 (0.9)
Other	2 (0.0)	8 (0.1)	6 (0.4)
Uterine corpus cancer (ICD-7; 172)	200 (0.2)	64 (0.7)	15 (1.0)
Ovarian cancer (ICD-7; 175.0)	97 (0.1)	31 (0.4)	18 (1.2)
Vulvar/vaginal cancers (ICD-7; 176)	25 (0.0)	6 (0.1)	1 (0.1)
All gynecological cancers	386 (0.3)	221 (2.6)	101 (6.5)

Abbreviation: ICD-7, International Statistical Classification of Diseases and Related Health Problems, 7th revision.

[a]Normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005.

[b]Atypical glandular cells of undetermined significance.

[c]Adenocarcinoma in situ.

[d]Start of follow up 3 months after the cervical smear; end of follow up 31 December 2013; number. of women 121 023.

[e]One case of cervical cancer was not histologically verified.

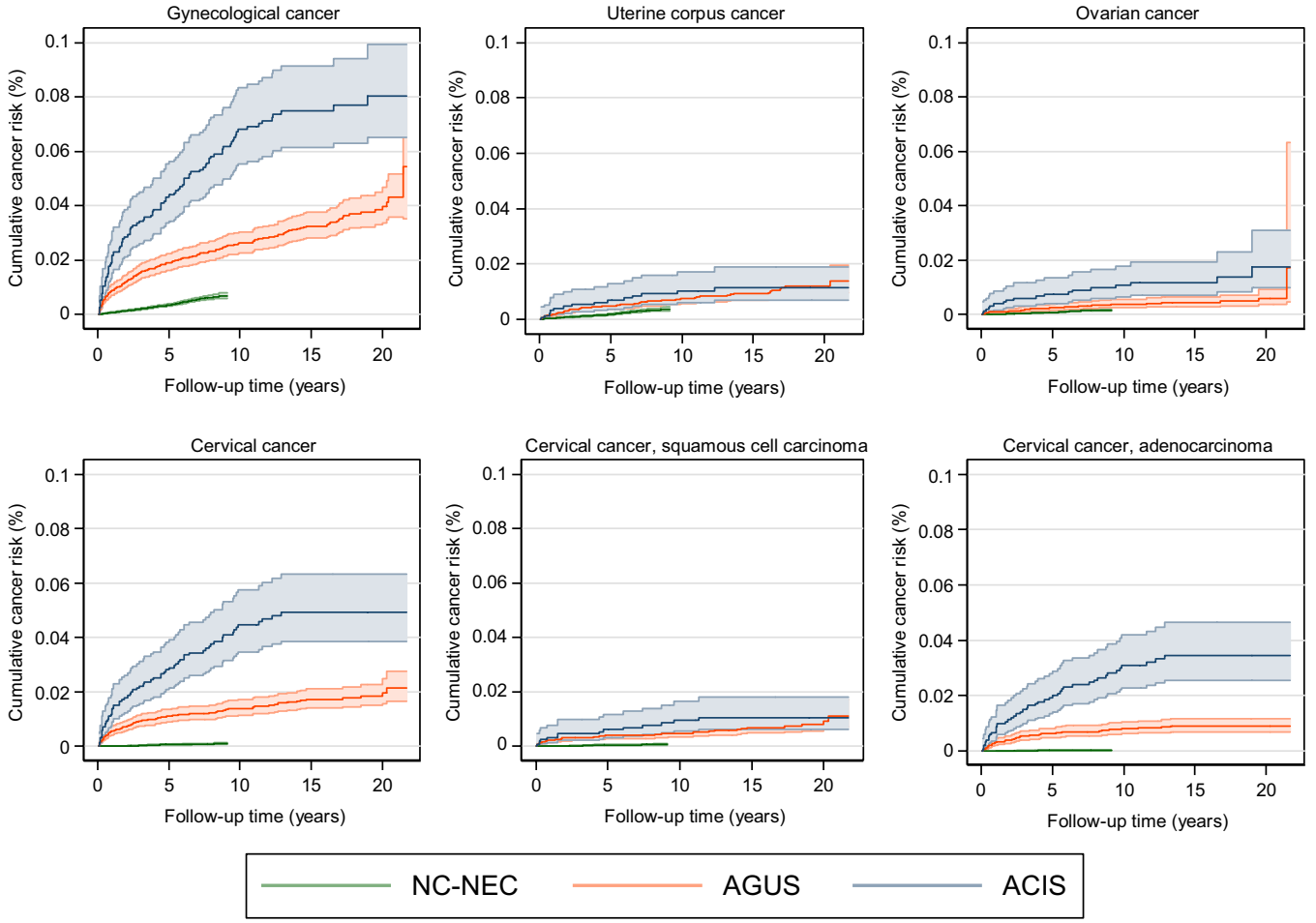

FIGURE 2 Cumulative risk of gynecological cancer according to cervical cytology, 1992/2005-2013. ACIS, adenocarcinoma in situ; AGUS, atypical glandular cells of undetermined significance; NC-NEC, normal/benign cells, but absence of endocervical or metaplastic cells; recorded since 2005 [Color figure can be viewed at wileyonlinelibrary.com]

study by Scheiden et al[31] resulted in 29% endometrial adenocarcinomas. Zhao et al[30] also showed a relatively high proportion of endometrial cancer (27%). In our study, uterine corpus cancer constituted 29% of all gynecological cancers following AGUS cytology.

Studies have shown that only a minority of women (estimates vary from 28% to 44%) who developed cervical adenocarcinoma had a preceding AGC or AGUS smear. This might indicate that other measures besides better management of AGC or AGUS, such as HPV screening, have the potential to improve the prevention of glandular diseases of the cervix.[34]

In NCCSP, smears labeled NC-NEC are followed as normal smears with a recommended screening interval of 3 years. In our study, 3% of women with NC-NEC in cytology were followed with histology within 3 years, and almost 80% of these were normal or benign. Altogether 55, 116 and 65 women with NC-NEC, AGUS and ACIS in cytology, respectively, developed cervical cancer over time. Assuming that the women in the different cytology categories had a cervical cancer risk similar to that of the general female population, the expected numbers would have been 95, 17 and 4, respectively. Consequently, there seems to be no increased risk of cervical cancer in women with normal smears lacking endocervical or metaplastic cells. Also, other longitudinal studies have shown no increased risk of high-grade lesions or cancer in women with smears without sampling from the transformation zone.[23,35]

Our study was based on complete records of the results from all cytology (NC-NEC, AGUS and ACIS) and histology specimens from the CRN/NCCSP. Among the strengths of our study were the population-based design, including all women with AGUS, ACIS and NC-NEC in their first cervical cytology, and the follow up of women over time.

Despite the assessment of complete records from national registries, some of the outcomes were very rare, and provided small numbers. The number of cervical cancer cases, especially following NC-NEC, was low. Also, ACIS was a relatively rare cytological result, especially in women <35 years. Besides, histology diagnoses following AGUS and ACIS were recorded since 2002, but for NC-NEC only since 2005. Altogether, this limited our use of statistical tests and complicated the interpretation of results. Therefore, the majority of the results presented in our study were descriptive.

Histology was not available for all women, and in particular only for 3% of those with NC-NEC cytology, potentially leading to

verification bias. The indication for biopsy in this group of women is not known but may relate to other risk factors such as genital symptoms or clinical findings, and the rate of normal histology in the total population of NC-NEC women is therefore likely to be higher.

Our study did not include information on hysterectomy and/or oophorectomy. The rates of hysterectomy are, however, lower in Norway (1.2 per 1000) than other western countries, such as the USA (5.4 per 1000) or Italy (3.7 per 1000).[36]

Follow up started 3 months after the cervical smear when we evaluated the cumulative risk of gynecological cancer to leave out most prevalent cancers diagnosed immediately after the index screen from the analyses. The slope of the cumulative hazard curves show that diagnostic events are frequent in the beginning of follow up, so the absolute levels of observed risk are somewhat sensitive to the start of follow up. Starting follow up at 6 months instead of 3 months as a sensitivity analysis, the pattern of risk was similar, but with an up to 20% decrease in the absolute level (in cervical cancer after ACIS). Some prevalent cancers are still likely to be included in the analysis.

5 | CONCLUSION

In this nationwide population-based cohort study, 78% of AGUS and 92% of ACIS smears were followed by histology within 3 years. Of these, 42% of the histological findings following AGUS, and 75% following ACIS were dysplastic, premalignant or malignant. Approximately 27% and 71% of the histological findings were CIN3, ACIS or more severe (including metastases) following AGUS and ACIS cytology, respectively. Only 3% of the NC-NEC smears were followed with histology within 3 years, and of these, 77% were normal or benign. During follow up, 6.5% and 2.6% of women with ACIS and AGUS smears developed gynecological cancer, respectively, and cervical adenocarcinoma was the most common subtype. This indicates that a considerable risk is associated with ACIS and AGUS cytology, and such findings warrant careful gynecological evaluation. According to this study, closer follow up of women with NC-NEC may not be required.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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