High-grade cervical abnormalities and cervical cancer in women following a negative Pap smear with and without an endocervical component: A cohort study with 10 years of follow-up

Short title: Endocervical component and detection of high-grade cervical abnormalities and cervical cancer

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Abbreviations used:
ECC: Endocervical component
HGA: High-grade cervical abnormality
CIN2+: Cervical intra-epithelial neoplasia grade 2 or higher

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Brief description (75 words) of the novelty and impact of the work:

Detection of high-grade abnormality (HGA) in Pap smears without an endocervical component (ECC) may be less sensitive than in smears with an ECC. Few cohort studies have examined this possibility and even fewer have assessed whether cervical cancer rates are higher following a smear without an ECC. We conducted a cohort study in Victoria, Australia and found no evidence that the incidence of HGA or cancer was increased following Pap smears without an ECC.

Introduction

Substantial reductions in cervical cancer incidence and mortality have been achieved in most developed countries, including Australia, through organized screening programs based on Papanicolaou (Pap) smears.[1] The objective of taking a Pap smear is to sample the transformation zone (TZ) and detect precancerous lesions, if present, and treat them before they develop into cancer. The TZ is the area of the cervix where the transformation from the columnar epithelium to squamous epithelium takes place and is the site where most cervical cancers and intraepithelial lesions develop.[1] The presence of columnar cells (also known as endocervical cells or an endocervical component (ECC)) in the smear, although not required for a smear to be 'satisfactory for evaluation', is an indication that the TZ has been sampled[2] and traditionally considered an indicator of specimen adequacy.[3]

Most cross-sectional studies show that the prevalence of cervical intraepithelial neoplasia (CIN) is lower in smears without an ECC (ECC-) than in smears that have an ECC (ECC+).[4-7] Case-control studies of smears that preceded a histologic diagnosis of CIN and that correctly predicted CIN were more likely to include the ECC than smears that failed to predict the CIN lesion, suggesting that false-negative results may be an issue.[8, 9] These findings have raised concerns as to whether Pap smears without ECC are less sensitive in detecting precancerous lesions and whether such women should be screened earlier than the recommended interval. However, early repeat testing of women without ECC in smears with normal cytology could only be justified if they are at increased risk of histologically confirmed high-grade cervical abnormality (HGA) and/or invasive cervical cancer.

Six previous cohort studies have followed women who had an initial normal (index) smear to determine whether their risk of a histologically-confirmed HGA or invasive cervical cancer was higher when the smear had no ECC.[10-15] All but one study [10] showed that women whose index smear had no ECC were at either lower or equal likelihood of having a subsequently detected cervical intra-epithelial neoplasia grade 2 lesion or higher (CIN2+) than women whose index smear contained an ECC. Only one cohort study had sufficient cases (n=243) to analyse incidence of invasive cervical

cancer; and in that study the incidence rate did not vary by ECC status of the index smear after eight years of follow-up (OR: 1.01 95% CI: 0.68 to 1.49).[13]

Although the ECC status of women's smears can vary, most cohort studies ignored smears after the index smear. Mitchell *et al* analysed data from the Victorian Cervical Cytology Registry and showed that the rate of histological CIN2+ for women whose index smear was ECC- but whose next smear was ECC+ had a slightly lower rate of histological CIN2+ than did women for whom both smears were ECC+ [age-adjusted rate ratio: 0.89, 95% CI: 0.67 to 1.12],[14] and concluded that early repeat testing of women whose negative smears lacked an ECC was not justified.[13-15] However, the analysis was conducted when the proportion of smears containing an ECC in Victoria was relatively stable or increasing over time. In Australia, the age-standardised proportion of smears containing an ECC declined from 82.1% in 2004 to 78.6% in 2011.[16] The reasons for this decline are likely to be multifactorial and may include changes in smear taking devices and changes in reproductive factors and hormone use over time.

Given the limited evidence that smears without ECC may be associated with reduced sensitivity, we undertook a retrospective cohort study to estimate rates of histologically confirmed HGA and cancer in women with negative Pap smears with and without ECC.

Materials and Methods

We analysed de-identified records from the Victorian Cervical Cytology Registry (VCCR), which is a voluntary "opt-off" confidential database of cervical cytology and histology reports in the state of Victoria, Australia.[17] Laboratories reporting cervical cytology provide the Registry with data on all Pap smears taken in Victoria, unless a woman chooses not to participate. The estimated "opt-off" rate is less than 1%.[17]

For this study, 5,880,322 Pap smears and 195,065 histology records from 1,688,432 women, performed between 1 January 2001 and 31 December 2010, were extracted. Women were eligible if they were 18-69 years of age at the time of their first Pap smear in this period, and had at least two Pap smears in the period, with the first smear (the index smear) showing no abnormality. Women were excluded if they had any record of a histological diagnosis of a HGA or cancer prior to 1 January

2001 (n=33,445 [6%]), or if they had a histological diagnosis of a HGA, or colposcopy or treatment on the same date as their index smear (n=1189 [0.2%]). We also excluded women with hysterectomy or other abnormalities on the same date as their index smear (n=4930 [0.9%]) and women whose results of a smear or histology were not available at the time of data extraction (n=24,129 [4%]). This left 1,119,630 women for HGA analysis and 1,119,740 women for cancer analysis. The difference was due to some women who were not included in the HGA analysis because they did not have a smear prior to receiving a histological diagnosis of HGA.

In Australia, all laboratories report cytology according to the Australian Modified Bethesda System (AMBS) 2004.[18] This coding allows reporting on both the squamous and endocervical component of the cervical cytology sample.[16] According to this coding system, a smear is not classified as unsatisfactory on the basis of the absence of an endocervical component alone.[18] A cytology result with no endocervical component means no endocervical cells are present and only squamous cells in the sample are assessed for abnormalities or cancer.[16] Histology is coded in-house and mapped to the national data dictionary of the National Cervical Screening Program.[16] Most coding is checked by a second staff member for quality assurance purposes.

We defined HGA as a histological diagnosis of a squamous lesion including CIN2, CIN3, micro-invasive and invasive squamous cell carcinoma, a glandular or mixed lesion including adenocarcinoma-in-situ (AIS), mixed adenosquamous/carcinoma-in-situ (CIS), micro-invasive and invasive endocervical adenocarcinoma, mixed adenosquamous carcinoma or other invasive cancer of the cervix. Separate analyses were performed for all HGA, for each morphological type of HGA, for all cancer, for each morphological type of cancer and for micro-invasive and type of invasive cancer.

Follow-up commenced at the index smear and ended at the first abnormal smear that preceded the diagnosis of histologically-confirmed HGA or cervical cancer, the date of the histological diagnosis in the absence of a preceding abnormal smear, date of hysterectomy, date of death, or 31 December 2010, whichever came first (referred to as the exit date). Ninety-eight percent of women had one or more abnormal smears prior to histologically-confirmed HGA or cancer diagnosis and more than three-quarters of women with a histological HGA or cancer, were diagnosed within one

year of the first abnormal smear, suggesting that smears taken after the first abnormal smear and prior to a histological diagnosis of a HGA or cancer were not likely to be for screening purposes.

Because the ECC status of women's smears can vary, the ECC status was treated as a time varying exposure, thus, follow-up was split at each smear after the index smear (i.e. multiple records per woman). At each time during follow-up, a woman's ECC status was determined by the ECC status of her most recent smear. For example, if a woman had an ECC+ smear on 16 March 2001 and an ECC- smear on 20 April 2003, she was classified as "ECC+" between these two dates and "ECC-" thereafter.

Poisson regression was used to estimate incidence rates and incidence rate ratios (IRR) for ECC status with adjustment for age and calendar year. For all IRRs, the reference category is ECC+. Restricted cubic splines were used to model the effects of age on rates of HGA and cancer.[19] Calendar year was fitted as a categorical variable. Interactions between ECC status and age and calendar year (i.e. the woman's age and the calendar year at the time of the smear determining current ECC status) were fitted to assess whether the IRRs for ECC status changed with age or calendar time.

For consistency with analyses of other cohort studies, we also performed an analysis in which we ignored all smears after the index smear. We used logistic regression, with adjustment for age and calendar year at the time of the index smear, to estimate the odds ratio for a subsequent HGA (or cancer) in relation to the ECC status of the women's index smear over the entire period of available follow-up (to the exit date) for each woman. All analyses were conducted using Stata 11.1 (StataCorp, College Station, TX, USA).

Results

The final dataset for analysis included 3,949,999 negative smears from 1,119,630 women for the analysis of HGA and 3,950,956 negative smears from 1,119,740 women for the analysis of cancer. About three quarters (77%) of the smears were ECC+. The median [25th, 75th percentile] number of smears per woman was 4 [3, 5] with an average time between the smears of 2.1 years (SD 1.2) regardless of ECC status (Table 1). Figure 1 shows the proportion of smears without an ECC by calendar year and age (5 year age groups). Within each age group, the proportion of smears without

an ECC increased over calendar time. For women less than 40 years old, the proportion without an ECC varied little by age; thereafter the proportion increased with age until 65-69 years.

During follow-up, 13, 855 HGA were reported; of these 96.3% were squamous abnormalities, 3.5% were glandular/mixed abnormalities, and 0.2% were other cancers of the cervix. There were also 307 cancers; of these 49% were squamous cancers, 43% were glandular/mixed cancers and 8% were other cancers of the cervix (Table 1). The incidence rate of HGA decreased with increasing age (Table 2).

After adjustment for age and calendar year, the overall rate of HGA was about 30% lower following ECC- smears (IRR 0.69, 95% CI 0.62-0.77, Table 3). However, the association was modified by age (p for interaction = 0.001), such that the IRR was close to unity at younger ages (e.g. 0.88, 95% CI 0.76-1.00 at age 20) and substantially less at older ages (e.g. 0.71, 95% CI 0.63-0.79 at age 45 years and 0.62, 95% CI 0.53-0.70 at age 55 years). Calendar time did not modify this association (p for interaction = 0.93). Figure 2 shows the predicted rates of HGA from the model with the interaction between ECC status and age – they diverge with increasing age. The overall IRRs were similar for squamous and glandular/mixed HGA (Table 3). For squamous but not glandular/mixed HGA, the IRRs decreased with increasing age.

In contrast, the incidence rate of cancer was slightly increased after ECC- smears (Table 2), although the adjusted IRR was not statistically significant (IRR 1.15, 95% CI 0.89-1.49) (Table 3). This association was limited to squamous cancers, especially invasive squamous cancer, albeit not statistically significant (IRR 1.61, 95% CI 0.96-2.68) and there was no association between ECC-smears and glandular/mixed or other types of cancer (Table 3). None of these associations were modified by age or calendar time (Table 3).

For the analysis in which all smears after the index smear were ignored, there was an average of 7.5 years of follow-up per woman. The odds ratios from the logistic regression, after adjustment for age and calendar year at index smear, were 0.78 (95% CI: 0.75-0.82) for HGA and 1.23 (95% CI: 0.94-1.60) for cancer.

Discussion

We found that the rate of histologically-confirmed HGA following a negative smear without an ECC was significantly lower than a negative smear with an ECC. This difference was greatest for older women. The rate of invasive cervical cancer was similar after smears without and with ECC; although the rate of invasive squamous cancer was modestly elevated after smears lacking an ECC, this did not reach statistical significance.

Our study has several strengths. It used a large population based registry that records almost all Pap smears in Victoria. The large sample size enabled us to estimate rate ratios for HGAs with high precision, although our estimates for cancer were less precise because cancer was an uncommon outcome. The study had long follow-up – an average of 7.5 years per woman and a maximum of 10 years, and more than 70% of the women had three or more negative smears. We excluded the time and any smears after the first abnormal smear as these smears were more likely to be taken as part of subsequent clinical management rather than for screening purposes.

Our analytic methods enabled us to more accurately classify the ECC status of women than has been the case in most cohort studies, which by ignoring smears after the index smear assumed that the ECC status of each subsequent smear was the same. If the misclassification of ECC status in those studies is non-differential, which seems likely, it could lead to attenuation of associations. If there are secular trends in the prevalence of smears without an ECC (as in Australia), ignoring subsequent smears will underestimate the proportion of women who have a smear without an ECC, further contributing to potential bias. Our method is also more relevant to clinical practice, since it directly addresses the question of whether the screening interval following a negative ECC- smear should be varied. It is reassuring; however, that our preferred method of analysis gave similar results to the method equivalent to that used in other studies, suggesting that the results of those studies were not adversely affected by the assumption that ECC status remained the same throughout follow-up.

Our results are consistent with most other cohort studies, that is, no excess HGA or cancer following negative smears without ECC when compared to women with negative smears with ECC.[11-15] The results were similar whether studies used histological or cytological endpoints.[11, 12, 14] The only

exception to this was the study by Vooijs *et al*, which found significantly higher cytological abnormalities on the subsequent smear 3 years later for women whose initial smear lacked an ECC than for women whose initial smear included an ECC.[10] However, the results of this study should be interpreted with caution, because women with abnormalities in the index smear were not excluded from the analysis and it is difficult to determine if the increased risk of abnormalities in the subsequent smear was due to incident lesions or prevalent lesions missed in the initial smear or a mix of both. Additionally, this study by Vooijs *et al* was conducted in the 1980's when the use of better sampling devices was not widespread. With the advent of brooms and brushes the proportion of ECC+ smears increased without a corresponding significant increase in the detection of HGA.[20]

The clinical relevance of ECC has also been explored using weaker study designs, namely cross-sectional and case-control designs. These studies concluded that the presence of ECC in the smear is associated with increased detection of squamous abnormalities suggesting a higher sensitivity of smears with ECC.[4-9, 21] However, cross-sectional studies are limited primarily because it is not possible to determine if the increased detection of abnormalities in smears with ECC is due to the higher sensitivity of these smears or the presence of the lesions in the cervix that allows convenient sampling of the TZ (or ECC).[13, 15] The case-control studies [8, 22] and case-series studies [9, 21] of review of smears prior to histological diagnosis of CIN showed that endocervical columnar cells (that defines the ECC) were less likely to be present in false-negative smears compared to true positive smears; but the difference was not statistically significant. Hence, if smears without ECC were less sensitive and more likely to miss relevant lesions we would expect a higher frequency of HGA in the subsequent smears of such women.

Although cohort studies provide the strongest evidence, they have some limitations.[10, 14, 15]Most prior cohort studies were conducted during the time when ECC- smears required early repeat smears. Such studies are subject to ascertainment bias if there is differential follow-up for ECC- and ECC+ smears. If ECC- smears had more intensive follow-up it could result in increased detection of pre-invasive lesions in these smears and successful treatment of these lesions will result in a reduced incidence of invasive cancers. Bias is also possible in longitudinal studies with one subsequent smear

where only subsequent positive cytology is subjected to histological verification. Abnormalities may be missed on subsequent Pap smear without ECC and thereby less likely to be subjected to histological verification. Studies restricted to one subsequent smear or with short follow-up are more prone to this bias. In one longitudinal study when the ECC status of the subsequent smear was taken into account, prevalence of cytological abnormalities was significantly higher in smears with ECC when compared to smears without ECC in the subsequent smear;[12] more in line with the findings of the cross-sectional studies and verifying that bias is likely with short follow-up. This issue could only be definitively addressed if women with negative smears were verified by histology. Baer *et al* in their study subjected a random sample of HPV negative women with negative cytology to colposcopy and histology within 60 days of the initial negative smear.[23] The findings of this study were consistent with other longitudinal studies of no difference in CIN2+ lesions following negative smear without ECC when compared to negative smear with ECC.

Although we found no overall association with invasive cancer, we observed a modest non-significant increased risk of invasive squamous cancers associated with ECC negative smears. No significant association with cancer was observed in a previous cohort study by Bos *et al* where they reported that the risk of invasive cervical carcinoma within 8 years of initial negative smears without ECC was not elevated (odds ratio, 1.01; 95% CI: 0.68-1.49); however, it is unclear as to how the abnormal smears proximal to the highest histological diagnosis were handled in this study.[13] The apparent paradox of lower detection of HGA and a (non-significant) higher incidence of invasive squamous cancers in our study could be explained in two ways; firstly, given that the increase is not statistically significant it could be a chance finding, especially given that outcome-based subgroup analyses are subject to high false-positive rates and p-values in such cases should be interpreted with caution. In this case, the lower rate of HGA detection could be related to lower risk of HPV infection and subsequent cell transformation in women with ECC negative smears. A plausible explanation is that the TZ may be anatomically higher in the canal, where the endocervical cells are harder to sample (resulting in an ECC- smear), and the TZ is also less susceptible to HPV exposure, a known necessary precursor to the development of HG CIN and invasive cervical cancer. Secondly, it is plausible that if

ECC negative smears are associated with reduced sensitivity for CIN2+ at baseline, more CIN3+ or invasive cancer could be observed in subsequent follow-up. Treatment of CIN2 and CIN3 lesion is what prevents development of invasive squamous cancers. This finding (of a test with lower sensitivity detecting fewer CIN2+ at baseline, resulting in fewer lesions being indentified and treated, leading to higher rates of invasive cervical cancer at follow-up) has now been confirmed by large scale HPV vs. Pap smear randomised trials.[24, 25] A decrease in sensitivity of ECC negative smears for glandular lesions might be anticipated, as not sampling the transformation zone differentially misses glandular lesions, which might be expected to lead to an increase in glandular HGA and cancers. We did not observe this in our study and this may be due to the small number of glandular cancers or other factors such as difficulty in interpretation of abnormal glandular cells and unclear progression of glandular lesions to adenocarcinoma.[26] However, the issue warrants further exploration using data from other large registries with long follow-up.

The National Cervical Screening Program in Australia is currently under active review (due to report in 2014) and one of the options under consideration is primary HPV screening.[27] Introduction of primary HPV testing is likely to overcome sampling issues of cervical cytology as a screening test as the high risk HPV DNA test status is much more sensitive than cytology and less influenced by TZ sampling.[28] Cytology is likely to be used only as a triage test in this context and hence the relevance of the ECC would be greatly reduced. In addition, high risk HPV testing is likely to be more sensitive than cytology for detecting glandular lesions.[25, 29, 30]

In conclusion, our findings show that although there has been an unexplained decline in ECC+ rates over the last decade in Australia, detection rates of HGA remain significantly lower among women with negative smears without ECC and there was no increase in the overall rate of cancers following negative smears without an ECC. Based on the lack of evidence for an increase in invasive cervical cancer, the findings of this study do not support differential (accelerated) follow-up in women with a negative smear without an endocervical component.

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Table 1: Number of women, number of smears, endocervical status and number of high-grade abnormality (HGA) and cancers

Characteristics	HGA		All Cancers	
	Total	(%)	Total	(%)
Total Women	**1,119,630**	**100**	**1,119740**	**100**
2 smears	302,397	27	302,346	27
3 smears	250,556	22	250,563	22
4 smears	273,563	24	273,583	24
5 smears	206,499	18	206,520	18
6+ smears	86,615	8	86,728	8
Median [25th-75th percentiles] number of smears	**4 [3, 5]**		**4 [3,5]**	
Abnormalities	**13,855**	**100**	**307**	**100**
Squamous	**13,346**	**96.3**	**151**	**49**
CIN2	6,685	50	-	-
CIN3	6,562	49	-	-
Micro-invasive squamous cell Carcinoma	45	0.3	83	55
Invasive squamous cell carcinoma	54	0.4	68	45
Glandular/mixed	**485**	**3.5**	**131**	**43**
AIS	270	56	-	-
Mixed adenosquamous/CIS	104	21	-	-
Micro-invasive endocervical adenocarcinoma	13	3	23	18
Invasive adenocarcinoma	89	18	98	75
Mixed adenosquamous carcinoma	9	2	10	7
Cancer of the cervix-others	**24**	**0.2**	**25**	**8**
Total smears	**3,949,999**	**100**	**3,950,956**	**100**
ECC-	892,157	23	892,378	23
ECC+	3,057,842	77	3,058,578	77
Average time ±SD (in years) between smears				
ECC-	2.1 (1.2)		2.1 (1.2)	
ECC+	2.1 (1.2)		2.1 (1.2)	

Table 2: Proportion of smears and incidence rates of histologically diagnosed high-grade abnormality (HGA) and cancer by absence or presence of an endocervical component (ECC-/ECC+) and age at each smear

Age (years)	HGA						Cancer					
	ECC- (n=892,157)			ECC+ (n=3,057,842)			ECC- (n=892,378)			ECC+ (n=3,058,578)		
	Smears	(%)	n	Rate*	Smears (%)	n	Rate*	Smears (%)	n	Rate§	Smears (%)	n	Rate§
<20	11,245	(20)	37	3.91	44,457 (80)	124	3.26	11,250 (20)	0	0	44,473 (80)	0	0
20-24	55,019	(20)	552	5.47	214,227 (80)	2694	6.64	55,038 (20)	3	2.97	214,324 (80)	11	2.71
25-29	76,144	(20)	564	3.58	303,993 (80)	2898	4.49	76,180 (20)	9	5.71	304,134 (80)	31	4.81
30-34	95,253	(19)	451	2.25	394,021 (81)	2153	2.57	95,310 (19)	11	5.49	394,220 (81)	32	3.82
35-39	100,731	(19)	298	1.39	428,376 (81)	1485	1.60	100,755 (19)	12	5.57	428,484 (81)	39	4.19
40-44	103,477	(20)	161	0.76	415,182 (80)	941	1.05	103,499 (20)	8	3.78	415,246 (80)	24	2.68
45-49	105,857	(22)	99	0.47	375,523 (78)	565	0.70	105,876 (22)	4	1.88	375,577 (78)	25	3.10
50-54	102,591	(25)	51	0.25	316,245 (75)	283	0.42	102,606 (25)	7	3.45	316,265 (75)	20	2.97
55-59	95,845	(28)	39	0.20	250,521 (72)	198	0.37	95,853 (28)	6	3.14	250,536 (72)	16	2.97
60-64	79,070	(30)	20	0.13	181,033 (70)	116	0.30	79,077 (30)	4	2.51	181,041 (70)	15	3.85
65-69	55,627	(33)	25	0.21	114,316 (67)	78	0.30	55,631 (33)	8	6.81	114,322 (67)	13	5.04
≥70	11,298	(36)	5	0.07	19,948 (64)	18	0.13	11,303 (36)	4	5.87	19,956 (64)	5	3.73

*HGA rates are reported as per 1000 person-years;
§ Cancer rates are reported as per 100,000 person-years

Table 3: Incidence Rates and Rate Ratios comparing the rates of histologically diagnosed lesions in smears with and without endocervical components

Histologically diagnosed lesions, and types	No endocervical component			Endocervical component			Adjusted IRR (95% CI)□, p-value	Interaction p-value*
	Number	PY	Rate	Number	PY	Rate		
All HGA£†	2,302	1,845,335	1.25	11,553	6,554,533	1.76	0.69 (0.62-0.77); <0.001	0.001
Squamous	2,226	”	1.21	11,120	”	1.70	0.68 (0.60-0.76); <0.001	0.001
Glandular/mixed	70	’’	0.04	415	’’	0.06	0.64 (0.49-0.82); 0.001	0.976
All cancers€©	76	1,845,611	4.11	231	6,555,509	3.52	1.15 (0.89-1.49); 0.292	0.922
Squamous	40	’’	2.17	111	’’	1.69	1.28 (0.89-1.84); 0.181	0.463
Glandular/mixed	30	’’	1.63	101	’’	1.54	1.03 (0.68-1.56); 0.877	0.429
Others (cancer of cervix)	6	’’	0.33	19	’’	0.29	1.03 (0.41-2.60); 0.945	0.331
Severity of cancerα©								
Microinvasive	22	’’	1.19	84	’’	1.28	0.99 (0.62-1.59); 0.965	0.376
*Invasive*β©	48	’’	2.60	128	’’	1.95	1.27 (0.90-1.77); 0.164	0.686
-Squamous	22	’’	1.19	46	’’	0.70	1.61 (0.96-2.68); 0.069	0.932
-Glandular/mixed	26	’’	1.41	82	’’	1.25	1.08 (0.69-1.68); 0.778	0.482

£ includes cervical intraepithelial neoplasia grade II (CIN2), cervical intraepithelial neoplasia grade III (CIN3), micro-invasive and invasive squamous cell carcinomas (grouped as squamous HGA) and adenocarcinoma-in-situ (AIS), mixed adenosquamous/carcinoma-in-situ, micro-invasive and invasive adenocarcinomas, adenosquamous carcinomas (grouped as glandular/mixed HGA)

€ includes micro-invasive and invasive squamous cell carcinomas (grouped as squamous cancers) and micro-invasive and invasive adenocarcinomas, and adenosquamous carcinomas (grouped as glandular/mixed cancers) and cancer of the cervix-others

α includes micro-invasive squamous cell carcinomas and micro-invasive adenocarcinomas (grouped as micro-invasive) and invasive squamous cell carcinomas, invasive adenocarcinomas, and adenosquamous carcinomas (grouped as invasive)

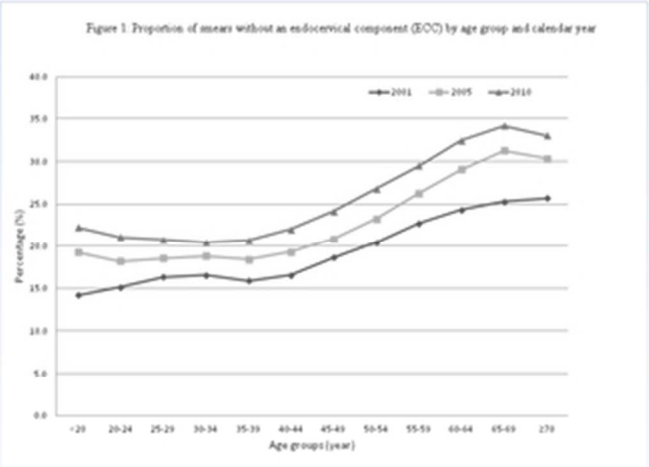
β includes invasive squamous cell carcinomas (grouped as squamous), and invasive adenocarcinomas, and adenosquamous carcinomas (grouped as glandular/mixed)

† All HGA rates are per 1000 person years

© All cancers and invasive cancers rates are per 100,000 person years

□ Incidence rate ratios (IRR) adjusted for age and calendar year

* p-value for interaction with age



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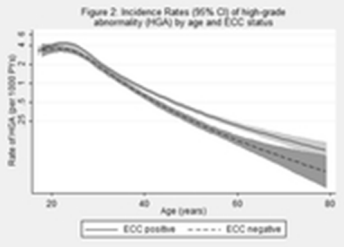

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