

Eleven-year review of data on Pap smears in Saudi Arabia: We need more focus on glandular abnormalities!

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BACKGROUND: We reviewed data from Saudi Arabia on epithelial cell abnormalities (ECA) detected by Pap smear after noticing a slight increase in the incidence of cervical glandular abnormalities in our regional laboratory in recent years.

OBJECTIVE: Clarify data on adenocarcinoma (ADCA) on Pap smears in Saudi Arabia.

DESIGN: Descriptive, retrospective study.

SETTINGS: Regional laboratory, Riyadh.

PATIENTS AND METHODS: We reviewed all Pap smears of adult females between 2006 and 2016 and compared our data with previously published results from Saudi Arabia.

MAIN OUTCOME MEASURE(S): Descriptive data on ECAs.

RESULTS: Among 19759 cases, atypical squamous cell of undetermined significance (ASC-US) was the most prevalent ECA (1.16%). ADCA occurred more than squamous cell carcinoma (SCC). In a comparison of published data before 2014 and after 2014 (including ours), there was a significant rise in ADCA (28 vs 48 cases; $P=.004$) with a significant drop in SCC, high-grade squamous intraepithelial lesions (HSIL) and low-grade squamous intraepithelial lesions (LSIL) ($P<.0001$, $.004$, and $<.0001$, respectively).

CONCLUSION: We recommend that pathologists and cytotechnologists be vigilant in screening Pap smears in our population, particularly for glandular abnormalities. We also recommend use of Pap smears in the initial workup of women with suspected gynecological abnormalities, regardless of evolutions in HPV testing.

LIMITATIONS: The pooling of data instead of analyzing by study year.

The Papanicolaou (Pap) smear is used to screen for squamous cell carcinoma (SCC) of the uterine cervix.¹⁻⁵ This technique helped to tremendously reduce the frequency of cervical cancer worldwide. Nowadays its main use is to screen for precancerous lesions.⁶⁻⁸ Human papillomavirus (HPV) has also been proven to be one of the most important etiological factors for cervical carcinoma development, both squamous and glandular.⁹⁻¹⁵ Other benefits of the Pap emerged including, but not limited to, detection of endocervical and endometrial adenocarcinoma (ADCA).¹⁶⁻¹⁸

The variation in cervical cancer frequency between countries, and sometimes within a given population,

can be related to many factors including the prevalence of HPV, lifestyle and socioeconomic status, and also sexual behavior.¹⁹⁻²¹ In the Middle East, and particularly in Arab countries, because of social restrictions and behaviors, it is estimated that HPV is less prevalent than in Western countries, something that is reflected in the practice of obtaining fewer Pap smears and in cervical cancer screening rates.²¹⁻²⁸ In Saudi Arabia, cervical cancer is listed as the eighth most frequent cancer among women ages 15 to 44 years. According to the World Health Organization, 6.5 million Saudi women 15 years of age and older are at risk of developing cervical cancer.^{29,30} Unfortunately, most women in Saudi Arabia re-

main undiagnosed until advanced stage disease, which decreases survival rates.³¹ Because of the limited availability of high-risk HPV testing in most of these countries, Pap testing remains — and most likely will remain for years — as the gold standard tool for cervical cancer screening.

In 2003, Jamal et al presented their results on a relatively large series of Pap smears from Saudi Arabia. Since then, more cumulative data have appeared, most of which has shown a low prevalence of epithelial cell abnormalities (ECA).³²⁻³⁹ In 2007 Abdullah et al published data from Saudi Arabia that demonstrated a 4% frequency of ADCA when compared to 9% for SCC among abnormal Paps in a set of 5590 Pap smears.³⁷ A relatively large study published by Al-Kadri et al, in 2015, from a central province in Saudi Arabia, demonstrated a higher frequency of ADCA (0.1%) when compared to SCC (0.04%) among a set of 19 650 slides.³⁸

In our daily practice we noticed a slight increase in the incidence of glandular abnormalities in recent years, something that no previous study has focused on.

PATIENTS AND METHODS

After obtaining approval from the institutional review board (IRB registration number H-01-R-053), a retrospective review of all Pap smear results for a period of 11 years (January 2006 to December 2016) was conducted using the electronic archives of cytopathology at the Riyadh Regional Laboratory at King Saud Medical City, in Riyadh, Saudi Arabia. Only ECA diagnoses were

filtered, which were later revised by the participating group of pathologists. When a discrepancy occurred with the original diagnosis, the case was revised in a consensus meeting with complete agreement on the final diagnoses, and a corrective action taken whenever needed. For simplicity of data illustration, we grouped all glandular abnormalities, excluding adenocarcinoma in-situ (AIS) and invasive ADCA, as atypical glandular cells (AGC using the Using the 2001 Bethesda nomenclature scheme).⁴⁰ No additional information, tests or patient contact were needed; therefore patient consent was waived. After our data was gathered, a PubMed search was conducted online for all previously published results in Saudi Arabia pertaining to the study.

We pooled the data from studies done before 2014 and those from studies after 2014 including ours. A statistical analysis was conducted using the chi-square test. The statistical analysis was conducted using the chi-square test by hand calculation.

RESULTS

Among 19759 Pap smears, 391 cases (1.98%) showed ECA (mean [SD] age, 39 years) (**Table 1**). The age range of the population was 22 to 75 years. We classified ECA cases into 230 atypical squamous cells of undetermined significance (ASC-US) (mean age, 37 years), 52 low-grade squamous intraepithelial lesions (LSIL) (mean age 39 years), 2 atypical squamous cells - cannot exclude high-grade lesion (ASC-H) (mean age 38 years), 46 high-grade squamous intraepithelial lesions (HSIL)

Table 1. Distribution of epithelial cell abnormalities over the past 11 years (N=391).

Year	Number of Pap smears	ASC-US	LSIL	ASC-H	HSIL	SCC	AGC	AIS	ADCA
2006	510	19	4	0	0	0	1	0	0
2007	1315	25	5	0	4	0	2	0	2
2008	2045	18	8	0	3	3	0	0	0
2009	2316	35	1	0	7	1	2	0	1
2010	2311	52	4	0	11	3	1	0	0
2011	2255	21	7	0	5	1	2	1	1
2012	2040	15	7	0	3	3	3	1	1
2013	1823	9	0	0	2	0	0	0	1
2014	1687	13	6	0	6	2	2	0	4
2015	1595	15	4	2	3	2	2	2	6
2016	1862	8	6	0	2	1	3	0	7
Total (%)	19759	230 (1.16)	52 (0.26)	2 (0.01)	46 (0.23)	16 (0.08)	18 (0.09)	4 (0.02)	23 (0.14)

Data are number of cases. ASC-US: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells-cannot exclude high grade, HSIL: High grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma, AGC: Atypical glandular cells, AIS: Adenocarcinoma in-situ, ADCA: Adenocarcinoma.

(mean age 42 years), 16 SCC (mean age 40 years), 18 AGC (mean age 44 years), 4 AIS (mean age 43 years), and 23 ADCA (mean age 45 years). An example from a HSIL, SCC, AGC, AIS and ADCA are shown in association with the corresponding histological tissue follow-up (**Figures 1-5**). Of the 391 cases, ASC-US was the highest percentage of ECA (1.16%). There was a relatively similar incidence of LSIL and HSIL among epithelial abnormal Paps (0.26% vs 0.23%, respectively). Most remarkable for us was the relatively higher incidence of ADCA (0.14%), being close to two-fold greater than that of SCC (0.08%). A steady rise in the diagnosis of ADCA in the latest years was also noted (starting in year 2014 and after).

In a comparison of our data to previously published studies (**Table 2**), we observed that the number of relatively large series published before 2014 (43 379 cases) was almost the same as those after 2014 (39 409 cases)

(**Table 3**). Most interesting to us was the remarkable difference in the prevalence of reported ADCA after 2014 when compared to previous results. There was a statistically significant drop in reported SCC, in comparison to a statistically significant rise in ADCA in recent years (P values of $<.0001$ and $.013$, respectively). There was also a significant drop in the reporting of LSIL and HSIL (P value of $<.0001$ and $<.004$, respectively). Only AIS had no statistically significant change ($P=.13$). Even when we combined neoplastic lesions (of at least in-situ carcinoma), we noted a statistical difference. HSIL and SCC in studies before 2014 were significantly higher, while studies during or after 2014 (including ours) showed a significant drop in such lesions, but a significant rise in neoplastic glandular lesions (**Table 3**).

DISCUSSION

Despite the remarkable drop in the frequency of cervi-



Figure 1A. Abnormal hyperchromatic squamous cells with a remarkable high N/C ratio diagnosed as HGSIL on Pap.

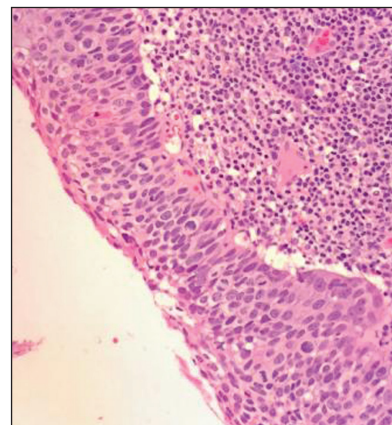


Figure 1B. The histological follow-up showed a squamous carcinoma in-situ.

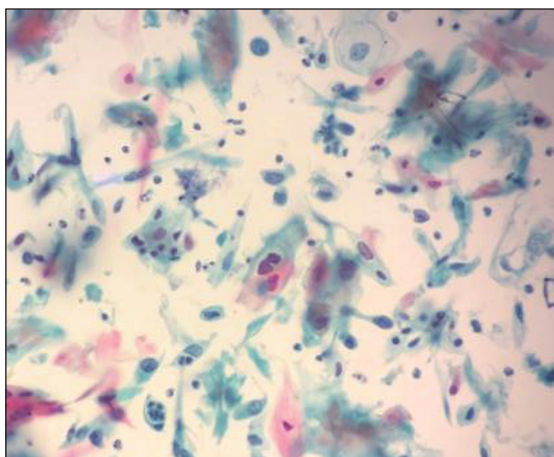


Figure 2A. Features deemed as SCC on Pap.

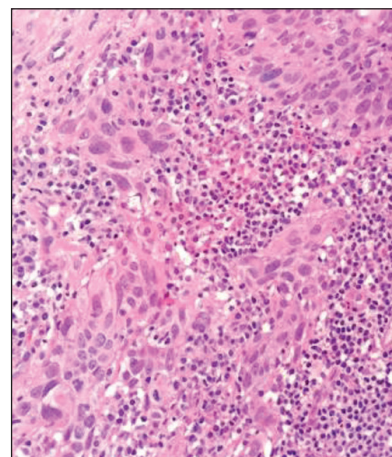


Figure 2B. Invasive SCC on histological follow-up.



Figure 3A. Abnormal-looking glandular cells diagnosed as AGC on Pap.

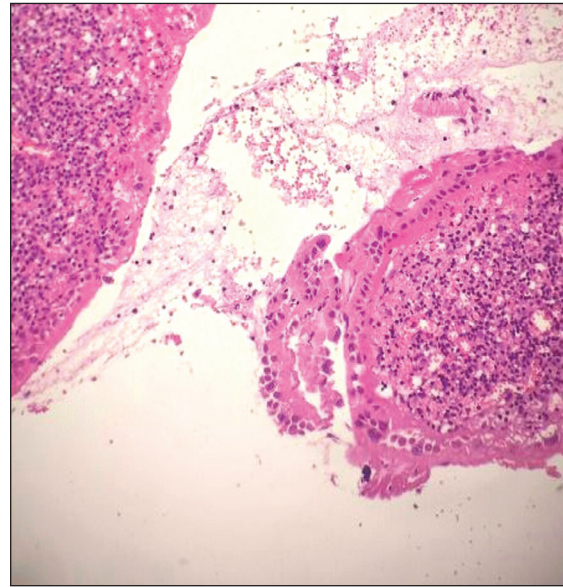


Figure 3B. The histological follow-up demonstrated an inflamed endocervical polyp.

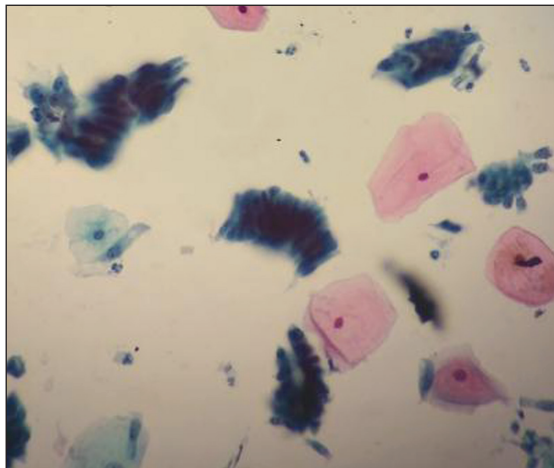


Figure 4A. Atypical and hyperchromatic columnar cells with remarkable cytoplasmic atypia and apoptosis deemed as AIS on pap.

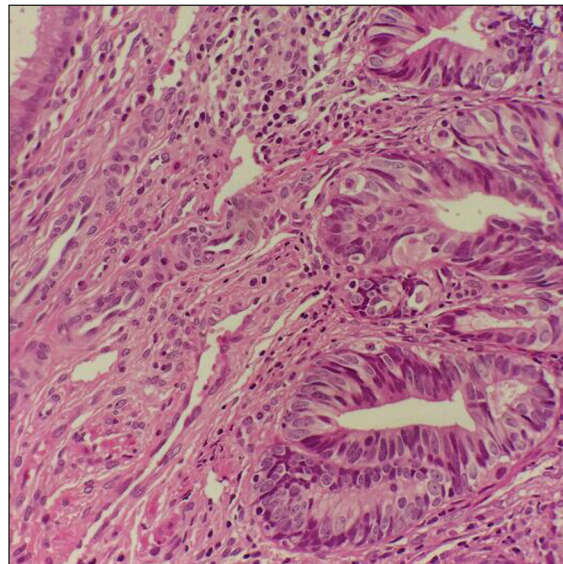


Figure 4B. Follow-up demonstrated AIS on biopsy tissue.

cal cancer over the past few years due to Pap screening protocols and the introduction of high-risk HPV testing and vaccines, the Pap smear is still a valuable test in the initial workup of women in the gynecological clinic, particularly in developing countries.⁴¹ A shift or a change in the initial approach or initial testing occurs from time to time with new guidelines being set and issued by the American Society for Colposcopy and Cervical Pathology based on emerging data; however, the aim of the Pap remains the same over time.⁴² Most of Pap

smears are done as a routine during the first visit after pregnancy or when a vaginal discharge or abnormal bleeding occurs.³⁸

Cervical cancer is reported to be the third most common gynecological malignancy in Saudi women with an estimated incidence rate of 1.9 cases per 100 000 women-years. An increase in the incidence of such cancer in Saudi women is anticipated. Nonetheless, more than 40% of such cases are diagnosed at advanced stages in comparison with 25% of cases in British Columbia,

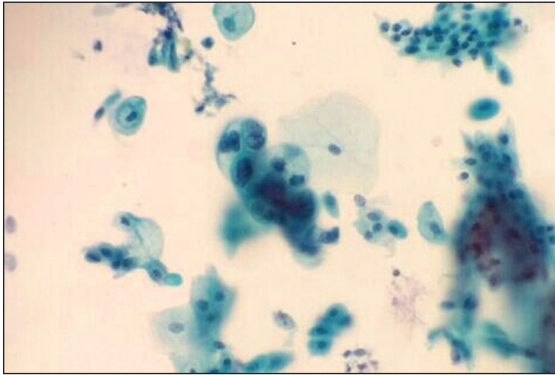


Figure 5A. Remarkably atypical glandular groups with prominent nucleoli, pleomorphic nuclei and vacuolated cytoplasm consistent with ADCA.

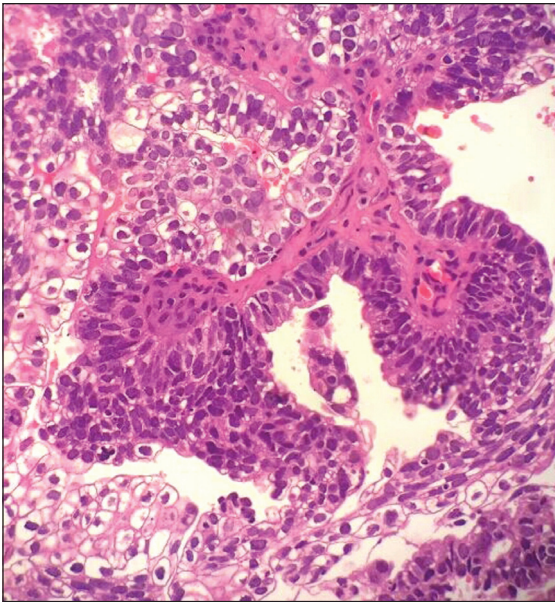


Figure 5B. Follow-up revealed an endometrial adenocarcinoma.

Canada. This is most probably attributable to the lack of a well-established national screening program in Saudi Arabia.^{31,43}

Based on our 11-year review of data, and the cumulative experience presented by others in the region over the past years, we highlight a rise in the frequency of detecting ADCA on Pap smears in our female population. At this time, no scientifically proven theory can explain these differences; however, we can postulate that this rise may be attributed to two main factors: First, the age group seeking medical attention in our community, leading to the detection of more ADCA, (particularly the occurrence of endometrial ADCA). This late presentation is shown in some of the studies

Table 2. Comparison of our results with previously published studies in Saudi Arabia.

Study	Cases	ECA	ASC-US %	LSIL %	ASC-H %	HSIL %	SCC %	AGC %	AIS %	ADCA %
Jamal et al (2003)*	22089	315 (1.4 %)	0.39	0.57	---	0.12	0.11	0.16	---	0.05
Elhakeem et al (2005)	2100	166 (7.9%)	2.76	1.3	0.19	0.66	0.33	2.66	---	---
Altaf et al (2006)	5132	241 (4.64%)	2.4	0.6	---	0.4	0.08	1.1	0.02	0.04
Abdullah et al (2007)	5590	261 (5%)	1.8	1.0	0.10	0.55	0.38	0.54	---	0.25
Balaha et al (2011)	1171	58 (4.95%)	2.99	0.09	0.6	0.68	0.34	0.25	---	---
Altaf et al (2012)	7297	1254 (17.3%)	9.3	2.7	0.8	0.9	0.06	3.40	---	---
Al-Kadiri et al (2015)	19650	841 (4.3%)	2.53	0.86	0.25	0.22	0.04	0.27	---	0.11
Nasser et al (2017) (current study)	19759	391 (1.98%)	1.16	0.26	0.01	0.23	0.08	0.09	0.02	0.14

*22 cases were labeled positive for malignancy and not subdivided in the table.

ECA: Epithelial cell abnormality, ASCUS: Atypical squamous cells of undetermined significance, LSIL: Low grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells-cannot exclude high grade, HSIL: High grade squamous intraepithelial lesion, SCC: Squamous cell carcinoma, AGC: Atypical glandular cells, AIS: Adenocarcinoma in-situ, ADCA: Adenocarcinoma.

Table 3. Comparison of data and statistical significance between results published in relation to year 2014 including ours.

Studies published in relation to year 2014	Cases	LSIL	HSIL	SCC	AIS	ADCA	HSIL+SCC	AIS+ADCA
Before (<2014)	43379	437	165	63	1	27	228	28
During or after - including ours (>2014)	39409	222	89	24	4	44	113	48
P value		<.0001	.004	<.0001	.13	.013	<.0001	.004

LSIL: Low grade squamous intraepithelial lesion; HSIL: High grade squamous intraepithelial lesion; SCC: squamous cell carcinoma; AIS: Adenocarcinoma in-situ; ADCA: Adenocarcinoma.

where the mean age was often more than 40 years.^{33,34} Second, pathologists with more experience have been reporting such lesions over the past few years, particularly with the influx of trainees—locals or expatriates—who had better exposure to such lesions in their training countries, particularly Europe, North America and Australia with higher Pap testing rates.

The study suffers from weaknesses. The choice of the year 2014, although being arbitrary, was based on the increase in ADCA diagnoses observed since that year. There is a statistical bias in data pooling; however, doing it year-by-year was not possible since most studies did not plot their results based on the year of diagnosis. Adding our data to the pool also affected

results, but an aim of the study was to demonstrate the variation in carcinoma diagnoses in recent years.

In conclusion, we recommend maintaining the Pap smear as a standard tool for screening, even after high-risk HPV testing is introduced, essentially so as not to miss glandular abnormalities. We also should enforce and encourage the training and vigilance of our screeners and pathologists on the atypical cytomorphological changes that can occur in glandular cells, the proper ways of reporting, and their clinical impact. Needless to say, good experience with glandular abnormalities is needed in our region; otherwise referral of cases for expert opinion is advised when experience is lacking.

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