Sultan Qaboos University Med J, February 2015, Vol. 15, Iss. 1, pp. e112–115, Epub. 21 Jan 15
Submitted 22 May 14
Revision Req. 14 Aug 14; Revision Recd. 21 Aug 14
Accepted 2 Oct 14

BRIEF COMMUNICATION

Trends in Epithelial Cell Abnormalities Observed on Cervical Smears over a 21-Year Period in a Tertiary Care Hospital in Kuwait

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الاتجاهات المحدّدة في تشوّهات الخلايا الظهارية المحدّدة عند إجراء المسحات العُنقيّة لمدة 21 سنة في مستشفى للرعاية العالية الاختصاص في الكويت

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ABSTRACT: ***Objectives:*** This study aimed to analyse trends in epithelial cell abnormalities (ECAs) in cervical cytology at a tertiary care hospital in Kuwait. ***Methods:*** ECAs in 135,766 reports were compared over three seven-year periods between 1992 and 2012. Conventional Papanicolaou (Pap) smear tests were used in the first two periods and ThinPrep (Hologic Corp., Bedford, Massachusetts, USA) tests were used in the third. ***Results:*** Significant increases in satisfactory smears, atypical squamous cells of undetermined significance (ASCUS) and atypical glandular cells of undetermined significance/atypical glandular cells (AGUS/AGCs) were seen in the second and third periods (P <0.001). No significant increases were observed among low-grade squamous intraepithelial lesions (LSILs) or high-grade squamous intraepithelial lesions (HSILs) (P >0.05). An increase was noted in carcinomas between the first and second periods although a significant decline was seen in the third (P <0.014). ***Conclusion:*** Satisfactory smears, ASCUS and AGUS/AGC increased during the study period although no significant increases in LSILs, HSILs or carcinomas were observed.

Keywords: Cytological Techniques; Papanicolaou Smear; Epithelial Cells; Retrospective Study; Kuwait.

الملخص: الهدف: تهدف هذه الدراسة إلى تحليل اتجاهات تشوّهات الخلايا الظهارية (إي.سي.إيي) في فحص الخلايا العنقيّة داخل مستشفى للرعاية العالية الاختصاص في الكويت. **الطريقة:** تمّت مقارنة اتجاهات تشوّهات الخلايا الظهارية (إي.سي.إيي) الواردة في 135,766 حالة فيما بينها على مرّ واحد وعشرين سنة بين الفترة الممتدة من العام 1992 وحتى العام 2102م. وقد استخدمت فحوصات لطاخة عنق الرحم بابا نيكولاو التقليديّة في الفترتين الأولى والثانية ثم تمّت الاستعانة باختبارات عنق الرحم (هولوجيك كوربوريشن، بيدفورد، مساتشوستس، الولايات المتحدة الأميركية) في الفترة الثالثة. **النتائج:** أظهرت هذه الاختبارات زيادة كبيرة في المسحات العنقية وارتفاعًا في الخلايا الشاذة الصدفيّة غير المحدّدة (ASCUS) إضافة إلى خلايا غُدّية شاذة وغير محدّدة/خلايا غدّية شاذة (AGUS/AGCs) تمّ تحديدها في الفترتين الثانية والثالثة (P <0.001). لم تُسجَّل أية زيادة تُذكَر على صعيد الآفات الحرفشية داخل الظهارة منخفضة الدرجة (LSILs) أو الآفات الحرفشية داخل الظهارة المرتفعة الدرجة (HSILs) (P >0.05). تم تسجيل ارتفاع في السرطان الغدّي بين الفترتين الأولى والثانية على الرغم من تسجيل انخفاض هام خلال الفترة الثالثة (P <0.014). **الخلاصة:** سجّلت المسحات العنقية نتيجة مُرضية ومقبولة مع زيادة في ASCUS و AGC/AGUS طوال مدة الدراسة على الرغم من عدم تسجيل أية زيادة ملحوظة بالنسبة إلى LSILs و HSILs أو حتى ظهور أيّ سرطان غديّ.

مفتاح الكلمات: تقنيات فحص الخلايا؛ لطاخة عنق الرحم؛ خلايا ظهارية؛ دراسة استعادية؛ الكويت.

Cervical cancer is the fourth most frequently occurring cancer affecting women worldwide after breast, colorectal and lung cancers; it is also the seventh most common form of cancer overall, with an estimated 528,000 new cases worldwide in 2012.[1] Approximately 70% of the global burden of cancer falls on less developed countries, with more than one-fifth of all new diagnosed cases from India.[1] In developing areas, the highest age-standardised rates (ASRs) of cancer per 100,000 are in South and central America (33.5), sub-Saharan Africa (31.0) and south central and southeast Asia (26.5).[2] The lowest rates of cancer are reported in China (6.8) and in developed regions such as North America, Japan and Europe, which has an ASR of 4.5. Low incidences have also been observed in some developing areas, such as the Middle East, including Iran and Turkey.[2]

Cancer of the uterine cervix is the fifth most common cancer in Kuwaiti females (4.6%), with an ASR of 6.8.[3] Invasive cervical cancer is preceded by a spectrum of heterogeneous epithelial cell abnormalities (ECAs) over a long period. Identification of the relevant risk factors and prompt management of the precancerous lesions are important in the

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Table 1: Spectrum of cervical cytology smear diagnoses during three seven-year periods between 1992 and 2012 (N = 135,766)

	Period				*P* value		
	1 1992–1998	2 1999–2005	3 2006–2012	Total 1992–2012	Period 1 versus 2	Period 2 versus 3	Period 1 versus 3
Total, n	40,806	52,728	46,870	140,404			
Satisfactory smears, n (%)	38,079 (93.3)	51,990 (98.6)	45,697 (97.5)	135,766 (96.7)	0.001	0.001	0.001
Cytological diagnosis, n (%)							
ASCUS	587 (*1.54*)	1,363 (*2.62*)	1,262 (*2.76*)	3,212 (*2.37*)	0.001	0.183	0.001
AGUS/AGC	160 (*0.42*)	543 (*1.04*)	389 (*0.85*)	1,092 (*0.80*)	0.001	0.002	0.001
LSIL	400 (*1.05*)	487 (*0.94*)	410 (*0.90*)	1,297 (*0.95*)	0.094	0.540	0.026
HSIL	92 (*0.24*)	106 (*0.20*)	96 (*0.21*)	294 (*0.22*)	0.262	0.887	0.375
Carcinoma	28 (*0.07*)	60 (*0.12*)	30 (*0.07*)	118 (*0.09*)	0.060	0.014	0.764

ASCUS = atypical squamous cells of undetermined significance; AGUS = atypical glandular cells of undetermined significance; AGCs = atypical glandular cells; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

Italics indicate percentages from satisfactory smear tests.

prevention of invasive cancer of the uterine cervix. Several studies from Saudi Arabia, including a study of sub-fertile Saudi females, showed a low prevalence of ECAs; however, there was still a wide range of distribution (2.9–17.3%).[4,5] This range strongly correlates with the actual difference in the distribution of invasive carcinomas of the cervix in Saudi Arabia.[6] Other studies from the Arab world have also reported a significant variation in the rate of ECAs: 3.3–3.6% in the United Arab Emirates,[7,8] 4.2% in Kuwait,[9] 7.8% in Egypt[10] and 11.9% in Nablus, Palestine.[11] Most of these studies were completed using conventional Papanicolaou (Pap) smear tests, where the cervical smears were reclassified according to the revised 2001 Bethesda system.[12]

Mubarak Al-Kabeer Hospital is a tertiary care hospital which provides cytological diagnostic services to 15 hospitals, 17 clinics and practitioners both in the Hawally area and elsewhere in Kuwait. The aim of this study was to analyse the changing trends of ECAs observed in cervical smears at this hospital over a period of 21 years compared in three periods of seven years each.

Methods

This retrospective study was designed to review cervical cytology reports performed in the cytology laboratory of Mubarak Al-Kabeer Hospital over a 21-year period from January 1992 to December 2012. The first two seven-year periods (1992–2005) used conventional Pap smear tests whereas the third period (2006–2012) used ThinPrep (Hologic Corp., Bedford, Massachusetts, USA) smear tests. A comparison was made between the trends of ECAs seen in the three seven-year periods (1992–1998, 1999–2005 and 2006–2012). Unsatisfactory cytology reports were excluded from the study. These included smears with very few epithelial cells or those where the morphology of the cells was obscured by blood or severe inflammation. Smears were categorised as "satisfactory" when an adequate number of epithelial cells were clearly visualised, as per the guidelines of the Bethesda system.[12]

Cytological diagnoses were changed where required to the modified Bethesda classification system.[12] The following categories were used: normal/negative for intraepithelial lesions or malignancy (NILM); atypical squamous cells of undetermined significance (ASCUS); atypical glandular cells of undetermined significance/atypical glandular cells (AGUS/AGCs); low-grade squamous intraepithelial lesions (LSILs), including changes induced by human papillomavirus (HPV) infection; high-grade squamous intraepithelial lesions (HSILs), which included ASCUS results with possible HSIL (ASC-H), and carcinomas. Epithelial cell abnormalities comprising of ASCs, LSILs, HSILs were considered as cervical precursor lesions.

Data management, analysis and graphical presentation were completed using the Statistical

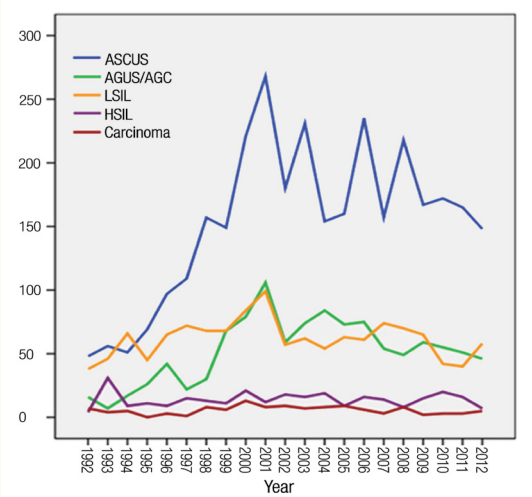

Figure 1: Trends in cervical cytology smear diagnoses in a tertiary care hospital in Kuwait between 1992 and 2012 (N = 135,766).

ASCUS = atypical squamous cells of undetermined significance; AGUS = atypical glandular cells of undetermined significance; AGCs= atypical glandular cells; LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion.

Package for the Social Sciences (SPSS), Version 20.0 (IBM Corp., Chicago, Illinois, USA). Descriptive statistics were presented as numbers, percentages and means ± standard deviations. The normal Z-test was used to test the difference in proportions and the Chi-squared test was used to determine if there was any trend in the proportion of cases over the 21-year period. The two-tailed probability value P <0.05 was considered statistically significant.

This study was performed according to the guidelines of the Combined Ethics Committee of the Faculty of Medicine, Health Science Centre and Ministry of Health in Kuwait, which conforms to the World Medical Association Declaration of Helsinki.

Results

During the 21-year period, a total of 140,404 cervical cytology smears were analysed in the cytology laboratory of Mubarak Al-Kabeer Hospital. Of these, 135,766 (96.7%) were found satisfactory for reporting [Table 1]. Overall, ECAs were observed in 4.43% of satisfactory smears; ECAs from the first, second and third seven-year periods were present in 3.32%, 4.92% and 4.79% of the smears, respectively. ASCUS were seen in 3,212 cases (2.37%), AGUS/AGCs in 1,092 cases (0.80%), LSILs in 1,297 cases (0.97%), HSILs in 294 cases (0.22%) and carcinomas in 118 cases (0.09%).

A significant increase (P <0.001) was noted in the proportion of satisfactory smears in the second and third period compared to the first (98.6% and 97.5% versus 93.3%, respectively) [Table 1]. Additionally, a significant increase was also observed between the first two combined periods (1992–2005) of conventional Pap smears in comparison to the third period (2006–2012) of ThinPrep smears (96.3% versus 97.5%, respectively).

With regard to cytological diagnoses, a significant increasing trend (P <0.001) was found among ASCUS and AGUS/AGC cases in the later periods compared to the first; AGUS/AGC cases were found to be more accurately identified using ThinPrep smears than with conventional Pap smears. No significant increase was observed among the number of LSILs and HSILs during the study (P >0.05). In carcinoma cases, an increase was observed between the first and second periods but a significant decline (P <0.014) was noted between the second and third periods [Figure 1].

Discussion

The distribution of ECAs in 140,404 cervical cytology smears analysed over a 21-year period did not show any significant change in LSIL, HSIL or carcinoma cases. The introduction of liquid-based cytology (LBC) during the final seven-year period (2006–2012) showed an increasing trend in satisfactory smears and the detection of ASCUS and AGUS/AGC cases.

In a population-based cervical cancer screening programme in Japan, disease detection rates were compared between specimens prepared by LBC and those prepared by conventional methods.[13] With the LBC method, the researchers found a significantly lower percentage of unsatisfactory specimens and a significantly higher positive rate of detection of tumour lesions.[13] However, Siebers *et al.* demonstrated in a large randomised controlled trial that the most common LBC method was not more effective in detecting cervical cancer precursors than well-performed conventional Pap smears; the prevalence of cervical intraepithelial neoplasms was equal in both study groups.[14] In a systematic review and meta-analysis comparing the two techniques, no incremental improvement in accuracy was demonstrated for the detection of high-grade cervical intraepithelial neoplasms using LBC versus conventional methods.[15] This was also observed in the current study as no statistically significant changes were observed for cervical precursors between cytology performed using conventional Pap smear tests and those performed using ThinPrep tests. Furthermore, Schiffmann *et al.* reported that both cytology methods provided similar risk stratification in predicting cervical cancer precursors.[16] They concluded that the choice of

cervical cancer screening method should be chosen on the basis of cost-effectiveness related to laboratory productivity, slide adequacy and the ease of ancillary molecular testing.[16]

Conclusion

Overall, ECAs were observed in 4.43% of cervical cytology smears analysed in a tertiary care hospital in Kuwait over a 21-year period. Satisfactory smears and the detection of ASCUS and AGUS/AGC cases were significantly increased during the seven-year period when ThinPrep smears were used. There were no statistically significant changes in the detection of LSILs, HSILs and carcinomas when LBC preparations were used as compared to conventional Pap smears.

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