CYTOLOGICAL SCREENING FOR PRECANCEROUS LESIONS OF THE CERVIX

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SYNOPSIS

This study was conducted to study the pattern and distribution of abnormal cervical smears detected in 41400 women who had cervical smears screened by two cytology laboratories over a one year period in 1985. The aim was to determine the prevalence of precancerous lesions of the uterine cervix as picked up through cervical smears. The age distribution according to the severity of the lesion, histological correlation and association suggesting a Human Papillomavirus infection are also presented. The main findings indicated a pick-up rate of 14 per thousand and 21 per thousand of abnormal smears detected from the two cohorts of women studied. The prevalence of carcinoma-in-situ was 3.0 and 3.6 per thousand smears screened. There was a high degree of correlation between cytology and histological confirmation. The prevalence of mild dysplasia or cervical intraepithelial neoplasia grade 1 was higher than that for carcinoma-in-situ and was 5.2 and 12.4 per thousand in the two groups of women respectively. In one group of women who were asymptomatic, 30% of the abnormal smears occurred under the age of 30 years. The results demonstrate the importance of cervical screening in the detection of early borderline lesions of cervical intraepithelial neoplasia.

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INTRODUCTION

Cervical cytology is the most promising procedure yet developed for the detection of early and unsuspected carcinoma-in-situ of the uterine cervix. As this method of screening has become more widely used, the question has been raised as to what effect it has had on the occurrence of invasive cancer and on mortality from the disease. The Singapore Cancer Registry has had complete population coverage and has compiled incidence rates of the commonest cancers in women from the years 1968–1982 (1). The Age Standardised Incidence Rate of 18.2 per 100,000 in the five-year period 1968–1972 has dropped to 16.5 per 100,000 in the years 1978–1982, where it has become the third commonest cancer in women after cancer of the breast and lung. It is difficult to determine the actual decline in this incidence without going into the epidemiological study of the aetiology and risk factors associated with the disease in the local context. However studies of cervical cancer screening programmes in other countries have shown a dramatic relationship between screening activities and the falling incidence of carcinoma of the cervix for instance in the Province of British Columbia (2). The British Columbia cohort study while not able to define exactly the frequency and rate of progression and regression of various degrees of pre-invasive change, did allow a better understanding of the natural history of pre-invasive disease and provided the observation that approximately 60% of patients with in-situ carcinoma of the cervix will progress to invasive disease if left untreated (3). Evaluation of the efficacy of cervical screening has been mainly by study of morbidity and mortality in a screened population, in which surgical removal of putatively precancerous lesions is expected to prevent invasive cancer of the cervix. Since the histological examination necessary for diagnosis and exclusion of invasive disease involves destroying what is being studied, the natural history of non-invasive lesions is largely inaccessible to direct observation. Intraepithelial precancerous changes form a progressive spectrum of abnormalities ranging from slight changes (early borderline lesions or mild dysplasia) to severe changes (carcinoma-in-situ). Separation of the various stages is at best arbitrary and introduces an extent of diagnostic variability among pathologists. It appears more reasonable to class all these lesions as "intraepithelial neoplasia" graded from I to III as suggested by Richart (4,5). The extent of preinvasive carcinoma of the cervix is difficult to determine. The incidence or pick-up is parallel to the intensity of the outreach to pick-up cervical cancer in its preclinical stage through cervical cytology screening programmes. The aim of this study is to present the results of the cervical cytological screening, as carried out by the Cytology laboratories of the Singapore Government Medical Service on government hospital patients and family planning acceptors of the Maternal and Child Health clinics, in determining the prevalence of precancerous lesions of the cervix picked up through cervical smears.

MATERIAL AND METHODS

In 1985 a total of 41,440 cervical smears were examined at the cytology laboratories of the Singapore Government Medical Service. The two participating laboratories were the Cytology Laboratory based at Kandang Kerbau Hospital and the Cytology Unit based at the headquarters of the Singapore Family Planning and Population Board. Both laboratories have since been relocated to the Department of Pathology, Outram Road. The cytology laboratory of Kandang Kerbau Hospital received 20,800 smears which were taken from gynaecological and obstetric in-patients and out-patients of Kandang Kerbau Hospital, Toa Payoh Hospital and Alexandra Hospital, and from prostitutes under surveillance for sexually transmitted disease at Middle Road Hospital (Table 1). 20,640 smears were screened at the Cytology Unit of the Family Planning and Population Board.

TABLE 1: PERCENTAGE DISTRIBUTION OF PATIENTS SCREENED BY HOSPITAL — 1985 CYTOLOGY LABORATORY, DEPARTMENT OF PATHOLOGY

Hospital	No. of Smears Screened	Percentage
Kandang Kerbau Hospital	17851	85.8%
Toa Payoh Hospital	1351	6.5%
Alexandra Hospital	1295	6.2%
Middle Road Hospital	302	1.5%
Singapore General Hospital	1	0.1%
Total	20800	100.0%

They were taken from asymptomatic women on the family planning programme of the Board and family planning acceptors from 23 Maternal and Child Health Clinics run by the Primary Health Care Division of the Ministry of Health. These family planning acceptors were either on oral contraceptive pills or were using one form or other of contraceptive devices. Of these, 7169 women were having their first smear whilst the others were follow-up cases with either annual or biennial repeat smears.

All smears were fixed in 95% ethyl alcohol, stained by the Papanicolaou method and screened by trained laboratory technicians. Abnormal or doubtful smears were referred to the Pathologists trained in cervical cytology for further evaluation. All smears were classified by both numerical and descriptive systems. The numerical code system used was according to the Systematised Nomenclature of Medicine (SNOMED). The cytology reports incorporated cytodiagnostic terminology with the use of a description in cytologic terms and a prediction of the histological condition. It incorporated the use of both the cervical intraepithelial neoplasia nomenclature (grades 1 to 3) and the dysplasia classification (mild, moderate and severe or carcinoma-in-situ) (6,7).

The definition of "abnormal smear" in this study was taken to include smears with dyskariotic and/or malignant cells and with cytologic features of dysplasias, cervical intraepithelial neoplasia (all grades), invasive squamous cell carcinoma and adenocarcinoma. Also included were smears with cytologic features reflecting the Human Papilloma Virus infection. The latter term was used synonymously with wart virus infection, condylomatous lesion and koilocytotic atypia (K.A.). These smears were scrutinised for the cytologic criteria as elaborated by Meisels et al (8,9), Koss (10), Syrjanen et al (11), Purola et al (12).

In the case of family planning acceptors with abnormal smears, recommendations were made for them to be referred to the gynaecological clinics of hospitals for colposcopic studies and biopsies. A repeat smear was requested for acceptors with CIN 1 (mild dysplasia) and if the subsequent smear

colposcopy. If the smear was normal the patient was requested to return in six months for a repeat smear.

Colposcopic directed biopsies were performed and classified according to the World Health Organization System with translation to the cervical intraepithelial neoplasia (CIN) grades of severity (13). The presence of condylomatous lesions in isolation or co-existing in juxtaposition or intermingled with dysplastic and neoplastic epithelium was recorded.

The histologic criteria for condylomatous lesions were based on that described by Meisels (8,9) and Reid (14).

RESULTS

Prevalence of Abnormal Smears

Abnormal cervical smears suggestive of the presence of cervical intraepithelial neoplasia grades 1, 2 and 3, condylomatous lesions and invasive carcinoma of the cervix were found in 441 of 20640 family planning acceptors and 297 of 20800 hospital patients (Table 2). The overall pick up rates of these condylomatous, pre-invasive and malignant lesions of the cervix were 21 per thousand in family planning acceptors and 14 per thousand in hospital patients. A break-down of the prevalence of abnormal smears according to the grade of severity of the dysplasia or cervical intraepithelial neoplasia showed that the prevalence of abnormal smears reflecting C1N1 or mild dysplasia amongst family planning acceptors was 12.4 per thousand (Table 3) and this was more than double that detected from hospital patients (5.2 per thousand). The prevalence of CIN 3 in each set of patients was similar at 3 per thousand for family planning acceptors and 3.6 per where invasive carcinoma of either squamous carcinoma or adenocarcinoma were suspected for asymptomatic family planning acceptors. Of these, seven had known histological diagnoses at the time of data compilation and were confirmed as carcinomas.

TABLE 4: AGE GROUP DISTRIBUTION OF ABNORMAL SMEARS FAMILY PLANNING ACCEPTORS — 1985

Age Group	Cases Screened	Abnormal Smears No.	Abnormal Smears per 1000
Under 15	24	—	—
15 – 19	150	4	26.7
20 – 24	1686	50	29.7
25 – 29	4746	76	16.4
30 – 34	5130	87	17.0
35 – 39	5154	102	20.0
40 – 44	2008	53	26.4
45 – 49	1163	34	29.2
50 & above	549	24	43.7

Table 4 shows the prevalance rate of abnormal cytology according to age groups in family planning acceptors. It was not possible to compute in detail the prevalence of abnormal smears according to age group in the hospital patients because of relatively poor compliance in the supply of the information in request forms. However Table 5 shows the mean age in years of the patients with varying

TABLE 2: RESULTS OF CERVICAL CYTOLOGIC SCREENING 1985 OVERALL PICK-UP OF ABNORMAL SMEARS

Cytologic Diagnosis	Family Planning Acceptors No. of Smears	Family Planning Acceptors No. per 1000	Hospital Patients Smears	Hospital Patients No. per 1000
Total No. of smears	20640		20800	
CIN 1, 2 and 3 Condylomatous Lesions Carcinoma	441	21	297	14

TABLE 3: RESULTS OF CERVICAL CYTOLOGIC SCREENING 1985 PREVALENCE OF ABNORMAL SMEARS

Cytologic Diagnosis	Family Planning Acceptors No. of Smears	Family Planning Acceptors Per 1000 smears screened	Hospital Patients No. of Smears	Hospital Patients Per 1000 smears screened
Total No. of smears	20640		20800	
CIN 1, mild dysplasia	262	12.4	109	5.2
CIN 2, moderate dysplasia	61	3.0	37	1.7
CIN 3, severe dysplasia/carcinoma-in-situ	62	3.0	75	3.6
Condylomatous Lesions*	77	3.7	61	2.9
Carcinoma (squamous, adenocarcinoma)	16	0.8	44	2.0

*This includes cases of Koilocytotic Atypia (KA) and CIN.

TABLE 5: CERVICAL CYTOLOGY SCREENING 1985
AGE DISTRIBUTION OF PATIENTS WITH ABNORMAL SMEARS

Cytologic Diagnosis	Family Planning Acceptors				Hospital Patients			
	No.	Mean Age Years	Minimum Age Years	Maximum Age Years	No.	Mean Age Years	Minimum Age Years	Maximum Age Years
CIN 1	262	34	17	60	109	36.9	19	54
CIN 2	61	34	17	64	37	43.4	26	57
CIN 3	62	33	18	52	75	40	23	75
Condylomatous Lesion only	40	31	21	48	35	36	22	60
Invasive Carcinoma	16	40	31	46	43	55	36	79

grades of severity of the lesion as detected on cytology. In the family planning acceptor group the youngest age at which abnormal cervical cytology was detected was 17 years. The highest prevalence rate of the dysplasias and carcinoma-in-situ during childbearing age (under 50 years) was between the ages of 20-24 with a pick up rate of 30 per thousand. In the younger age group of 15-19 the prevalence of abnormal smears was 27 per thousand. The average age of patients with dysplasias and carcinoma-in-situ was 34 and 33 years in family planning acceptors and 40.2 and 40 years in hospital patients. The average age for invasive carcinoma in the clinically unsuspected group of family planning acceptors was 40 years, and 55 years in the hospital patients.

Results of Histopathological diagnosis in cases with abnormal cytology.

The results of histopathological diagnosis in patients with abnormal cytology are summarized in Table 6 and Table 7. At the time of compilation of the results for the study 218 out of 297 hospital patients with abnormal smears and 189 out of 441 family planning acceptors with abnormal smears had further investigations including biopsies of the uterine cervix. Of the total of 128 cases of carcinoma-in-situ or CIN 3 suspected on cervical cytology, 116 had been biopsied and 115 patients had lesions ranging from condylomatous lesion to cervical intraepithelial neoplasia and invasive carcinoma on histology. The results indicate a high degree of correlation between cytology and histology when the cervical smears showed features of severe dysplasia or CIN 3. 88 patients (76%) had confirmed CIN 3, 13 patients (11%) had invasive carcinoma and the rest (13%) showed CIN 1 and CIN 2. 146 patients with smears showing features of at least mild dysplasia or CIN 1, had histological lesions ranging from condylomatous lesions to CIN 3 reflecting a correlation rate of 76%. 35 women (24%) had benign lesions without evidence of pre-invasive neoplasia or dysplasia. 33 (22%) women who had smears reflecting a lesser grade of dysplasia demonstrated the presence of a higher grade lesion of CIN 3 on histology. All the cases of invasive squamous cell carcinoma and adenocarcinoma of the cervix suspected on cytological smears were histologically confirmed when biopsies were taken.

Association of Human Papilloma Virus infection with dysplastic and neoplastic lesions

The cytologic smears were scrutinised with special attention to the detection of the cytologic pattern established as diagnostic of the Human Papilloma Virus (HPV) infection in the genital tract (8,11,12). Essentially 3 different cellular patterns characteristic of the genital wart infection were found: dyskeratotic superficial cells, koilocytes or "balloon cells" and condylomatous intermediate cells. The pick-up rate of smears with cytological

TABLE 6: HISTOLOGICAL DIAGNOSIS OF PATIENTS WITH ABNORMAL SMEARS
FAMILY PLANNING ACCEPTORS 1985

Cytologic Diagnosis	No. of Smears	No. with Histologic Diagnosis	Histologic Diagnosis					
			Benign	Condylomatous Lesions only	CIN 1	CIN 2	CIN 3	Squamous Carcinoma
CIN 1	262	70	18	6	24(18)	5(3)	16(9)	1
CIN 2	61	39	5	2	11(10)	15(13)	6(5)	—
CIN 3	62	56	—	2	1	5(5)	44(20)	4
Condylomatous Lesions only	40	16	3	6	7(5)	—	—	—
Squamous cell Carcinoma	16	7	—	—	—	—	2(1)	5
Total	441	188	26	16	43(33)	25(21)	68(35)	10

( ) With Condylomatous Lesion.
Histology known as at July 1986

HOSPITAL PATIENTS 1985

Cytologic Diagnosis	No. of Smears	No. with Histologic Diagnosis	Histologic Diagnosis						
			Benign	Condylomatous Lesions only	CIN 1	CIN 2	CIN 3	Squamous Carcinoma	Adeno-Carcinoma
CIN 1	109	76	17	10	22(10)	10(3)	17(3)	—	—
CIN 2	37	23	1	—	5(1)	7(2)	9(3)	1	—
CIN 3	66	60	1	—	1(1)	5(2)	44(7)	8	1
Dysplasia NOS	9	9	2	—	—	1	4	2	—
Squamous Carcinoma	35	28	—	—	—	—	1	24	3
Adenocarcinoma	6	6	—	—	—	—	—	—	6
Condylomatous Lesions only	35	16	6	3	5(3)	1	1(1)	—	—
Total	297	218	27	13	33(15)	24(7)	76(14)	35	10

( ) With condylomatous lesion.

features suggesting Human Papilloma Virus infection was 3.7 per thousand for family planning acceptors and 2.9 per thousand for hospital patients (Table 3). 77 smears out of 441 smears (17.5%) taken from family planning acceptors showed cytologic changes of HPV infection. 61 smears out of 299 smears (20.4%) taken from hospital patients had similar changes reflecting HPV infection. The biopsies of patients with abnormal smears were examined for histological evidence to suggest a condylomatous lesion either intermingled with or coexisting in juxtaposition to a dysplastic or neoplastic epithelium. Out of a total of 189 biospies, 104 (55%) showed evidence of Human Papilloma Virus infection in the histological sections in family planning acceptors and 49 out of 218 (22%) in hospital patients (Tables 8,9). A breakdown of the distribution according to the grade of severity of the cervical intraepithelial neoplasia illustrated the higher association with early lesions as mild dysplasia/CIN 1 (76%) compared to CIN 3 (51%) for instance in the family planning acceptors.

DISCUSSION

This study confirms the efficacy of the cervical smear in detecting precancerous lesions of the uterine cervix. Hitherto most studies in the past on results of cervical cancer screening in Singapore have given information on the smear pick-up rate of confirmed cases of carcinoma, both invasive and in-situ. Mao in a study of the results of screening of women attending the Family Planning and Population Board's family planning clinics from the years 1967–74 found a smear pick-up rate of 2.3 cases of confirmed carcinoma per thousand smears screened (15). In a study of cytological screening for cervical cancer in hospital patients, Sng found a pick-up rate of suspicious and positive smears to range from 9 to 25 per thousand during a three year period but the overall prevalence of histologically confirmed carcinoma-in-situ was 3.9 per thousand women screened (16).

The designation of type of abnormality is consistent with the trends to much more specific interpretation of cytologic abnormalities, particularly in reference to the various benign atypias, the specific categorization of dysplasia and cervical intraepithelial neoplasia and it eliminates much of the ambiguity of a rather broad and nonspecific "suspicious" category. Considerable difficulty has been encountered in analysing and correlating follow-up data in registries in a "number" system of reporting of abnormalities, such as the original I, II, III, IV system of Papanicolaou. It is very difficult to place the

TABLE 8: HISTOLOGICAL DIAGNOSIS OF PATIENTS WITH ABNORMAL SMEARS FAMILY PLANNING ACCEPTORS 1985

Histological Diagnosis	No.	With HPV	
		No.	%
Benign	26	—	—
CIN 1	43	33	76
CIN 2	25	21	84
CIN 3	68	35	51
Condylomatous lesion only	16	16	—
Invasive Cancer	10	0	—
Total	189	105	

TABLE 9: HISTOLOGICAL DIAGNOSIS OF PATIENTS WITH ABNORMAL SMEARS HOSPITAL PATIENTS 1985

Histological Diagnosis	No.	With HPV	
		No.	%
Benign	27	—	—
CIN 1	33	15	45
CIN 2	24	7	33
CIN 3	76	14	18
Condylomatous lesion only	13	13	—
Invasive Cancer	45	0	—
Total	218	49	

more specific abnormalities as currently reported into such a numerical system in a satisfactory or uniform manner. The British Society for Clinical Cytology set up a working party to define and recommend terms for general use in cervical cytology. The recommendation that a cytology report should consist of a concise description of cells present in clearly defined and generally accepted terms, a prediction of the histological conditions, and a recommendation for further management of the patients, should appeal to cytopathologists and clinicians alike (17,18).

The degree of severity of the histological lesion as suggested by the cervical smear assists in the decision of further management of the patient and with the advent of colposcopically directed biopsies, the clinician is able to confirm and eradicate precancerous lesions (19).

The prevalence of abnormal smears in this study was 21 per thousand in patients from family planning clinics and 14 per thousand in hospital patients. Where the pick-up rate for CIN 3, severe dysplasia or carcinoma-in-situ for each set of patients was similar i.e. 3.0 per 1000 and 3.6 per 1000, there appears to be a substantial increase in the incidence of CIN 1 or mild dysplasia and CIN 2 or moderate dysplasia in the family planning acceptors. The combined figures of CIN 1 and CIN 2 as picked up on smears from family planning acceptors was 15.4 per thousand against 6.9 per thousand in hospital patients (Table 3). The family planning acceptors were women who were asymptomatic and the majority were young women or women in the child-bearing age. 73% of the smears were taken from women in the age group 15-39 years. Thus the prevalence of abnormal smears in the cohort is significant. In the age group distribution study of abnormal smears there was a pick-up rate of 27 per thousand and 30 per thousand of abnormal smears in women in the age groups of 15-19 years and 20-24 years, and 30% of the abnormal smears occurred under the age of 30 years. Although invasive cervical carcinoma no longer ranks as the most common malignancy amongst women, largely due to the advent of cervical cytologic screening programmes (2), the incidence of carcinoma of the cervix appears to be increasing in some areas, even in Canada, primarily because of an increase in carcinoma of the cervix in younger women (20). During this same period, there has been a dramatic increase in the incidence of carcinoma-in-situ and cervical dysplasia, again in younger women (21,22).

These findings suggest that an increased frequency of smears in the younger women should not be reduced at the expense of the older women, who still contribute most to the numbers of invasive carcinoma and deaths. The average age for the invasive carcinoma in the clinically unsuspected group of family planning acceptors was 40 years and reflects an occult invasive stage.

Epidemiologic, morphologic and immunovirologic data have shown a close association between the Human Papilloma Virus and lower female genital tract carcinogenesis (9,11,23). The Papilloma Viruses have been classified according to their restricted host range and relatedness of DNA, with different HPV types having different oncogenic potential (24). The infections in the cervix are mostly subclinical and are associated with cervical dysplasias and cancers, although the causative role has yet to be delineated (23,25).

The histological prevalence in family planning acceptors of HPV lesions with carcinoma-in-situ was 51% and 76% in lesions of mild dysplasia. The figures were lower for hospital patients.

Studies of the distribution of HPV infections according to the grade of severity of the cervical intraepithelial neoplasia illustrate a higher frequency of morphological changes seen with the early lesions of mild dysplasia/CIN 1 compared to carcinoma-in-situ/CIN 3 (Table 10) (26–29). A similar observation has been made in this study. Cervical cytology has been a way to detect HPV infection of the lower female genital tract through the identification of viral cytopathic changes in cervical smears.

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REFERENCES

1. Waterhouse J, Muir C, Shanmugaratnam K, Powell J (eds): Cancer incidence in five continents. 4th edition, IARC, Lyon, 1982.
2. Allen HH, Anderson GH, Boyes DA et al: Cervical Cancer Screening Programme. Summary of 1982 Canadian Task Force Report. Department of National Health & Welfare. Canadian Med Ass J 1982; 127:581–9.
3. Boyes DA, Morrison B, Know EG, Draper GJ, Miller AB: A Cohort Study of Cervical Cancer Screening in British Columbia. Clin Inves Med 1982; 5:1–29.
4. Richart RM: The natural history of cervical epithelial neoplasia. Clin Obstet Gynecol 1967; 10:748–84.
5. Richart RM, Barron BA: A follow-up study of patients with cervical dysplasia. Amer J Obstet Gynecol 1969; 105:386–93.

TABLE 10: HISTOLOGICAL PREVALENCE OF CONDYLOMATOUS LESIONS

	No. of Biopsies	With Condyloma %	Dysplasia with Condyloma			Carcinoma-in-situ with Condyloma %
			CIN 1 %	CIN 2 %	CIN 1&2 %	
Bernstein (1985)	965	34	78	68	—	14
Meisels (1983)	927	60	—	65	—	47
Syrjanen (1983)	110	55	—	—	70	65
Grunebaum (1983)	348	22	34	37	—	13
Nyeem (1982)	531	19	—	—	35	8
Ludwig (1980)	675	22	—	—	50	32
Singapore Figs						
Family Planning (1985))	189	55	76	84	—	51
Hospital (1985)	218	22	45	33	—	18

6. Koss LG: Diagnostic Cytology and its Histopathologic basis. 3rd edition. Philadelphia. J B Lippincott, 1979.
7. Koss LG: Precancerous changes of the Epithelia of the Uterine Cervix. Compendium on Diagnostic Cytology. The Tutorials of Cytology. International Academy of Cytology. Eds: Wied GL, Koss LG, Reagan JW. 5th edition, 1983; 97–107.
8. Meisels A, Fortin R and Ray M. Condylomatous Lesions of the Cervix. II Cytologic, Colposcopic and Histopathologic Study. Acta Cytologica 1977; 21:3:379–89.
9. Meisels A, Moxin C, Casas-Cordera M: Human Papilloma Virus infection of the uterine cervix. Int J Gynecol Pathol 1982; 1:75–94.
10. Koss LG, Durfee GK: Unusual Patterns of Squamous Epithelium of the Uterine Cervix. Ann NY Acad Sci 1956; 63:1245–61.
11. Syrjanen KJ, Heinonen UM, Kauraniemi T: Cytologic Evidence of the Association of Condylomatous Lesions with Dysplastic and Neoplastic Changes in the Uterine Cervix. Acta Cytol 1981; 25(1) 17–22.
12. Purola E, Savia E: Cytology of Gynecologic condyloma acuminatum. Acta Cytol 1977; 21(2): 26–31.
13. Paulsen HE, Taylot CW, Sobin LH (eds): Histological Classification of Female Genital Tract Tumours. International Histological Classification of Tumours. Geneva. WHO 1975.
14. Reid L, Crum CP, Herschman BR et al: Genital Warts and Cervical Cancer. III. Subclinical Papilloma viral infection and cervical neoplasia are linked by a spectrum of continuous morphologic and biologic change. Cancer 1984; 53:943–53.
15. M Mao: Results of Cervical Cancer Screening by the Singapore Family Planning and Population Board, 1967–1974. FPPB Paper/38.
16. I Sng: Cytological Screening of Cervical Smears in Hospital Patients. Proc Obstet & Gynaec Soc 1972; 4:67–76.
17. Evans DMD, Hudson EA, Braun CL et al: Terminology in gynaecological cytopathology: report of the working party of the British Society of Clinical Pathology. J Clin Pathol 1986; 39:933–44.
18. H Fox: Cervical smears: new terminology and new demands. Br Med J 1987; 294:1307–8.
19. Soutter WP, Wisdom S, Brough AK and Monaghan JW: Should patient with mild atypia in cervical smears be referred for colposcopy. Br J Obstet & Gynaec 1986; 93:70–4.
20. Carmichael JA, Jeffrey JF, Steele HD and Oheke ID: The cytologic history of 245 patients developing invasive cervical carcinoma. Am J Obstet Gynecol 1984; 148:685-8.
21. Sadeghi SB, Hsieh EW & Gunn SW: Prevalence of cervical intraepithelial neoplasia in sexually active teenagers and young adults. Am J Obstet Gynecol 1984; 148:726–9.
22. Patterson MEL, Peel KR & Jaslin CAF: Cervical smear histories of 500 women with invasive cervical cancer in Yorkshire. Br Med J 1984; 289:896–8.
23. Coleman DV, Wickenden C & Malcolm ADB: Association of Human Papilloma Virus with Squamous Cell Carcinoma of the Uterine Cervix. Ciba Foundation Symposium 120, 1986. John Wiley & Sons, 175–89.
24. Howley PM: Papillomaviruses. Ciba Foundation Symposium 120, 1986. John Wiley & Sons, 243–46.
25. Gissman L & Schwarz E: Persistence and expression of Human Papilloma Virus DNA in genital cancer. Ciba Foundation Symposium 120, 1986. John Wiley & Sons, 190–7.
26. Ludwig ME, Lowel DM & Livolsi VA: Cervical condylomatous Atypia and its Relationship to Cervical Neoplasia. Am J Clin Pathol 1981; 76:255–62.
27. Nyeem R, Wilkinson EJ, Groves LJ: Condylomata Acuminata of the Cervix: Histopathology and Association with Cervical Neoplasia. Int J Gynec Pathol 1982; 1:246–57.
28. Bernstein SG, Voet RL, Guzick DS, et al: Prevalence of papillomavirus infection in colposcopically directed cervical biopsy specimens in 1972 and 1982. Am J Obstet Gynecol 1985; 151:573–81.
29. Grunebaum AN, Sedlis A, Sillman F, Fruchter R, Stanek A & Boyce J: Association of Human Papillomavirus Infection with Cervical Intraepithelial Neoplasia. Obstet Gynecol 1983; 62:448–55.