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Carcinoma of the uterine cervix: a review of its pathology and commentary on the problem in Malaysians

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Abstract

Since its recognition about 150 years ago, there has been much progress in the understanding of the pathogenesis, prevention, early detection and management of carcinoma of the uterine cervix. Important historical landmarks include the (1) recognition of pre-invasive and pre-clinical lesions, and the devise of various systems for reporting these lesions, (2) improvements in diagnostic techniques particularly colposcopy, (3) advent of therapeutic procedures (electrocoagulation, cryotherapy, laser therapy and loop electrosurgical excision), and (4) recognition of the aetiological relationship between the human papillomavirus and cervical neoplasia. The susceptibility of the cervical transformation zone to malignant change is now well recognised. The WHO classification system remains the one most commonly utilised for histological reporting of cervical cancers. In the recent 1994 update, cervical carcinoma is divided into 3 main categories: squamous cell carcinoma, adenocarcinoma and other epithelial tumours. Squamous cell carcinoma (60-80%) predominates among invasive cervical carcinoma. Recognised variants include verrucous, warty (condylomatous), papillary squamous (transitional) and iymphoepithelioma-like carcinoma. Adenocarcinoma (5-15% of invasive carcinomas) showsan increasing trend in young females. Like its squamous counterpart, preinvasive and microinvasive versions are known. Variants such as mucinous, endometrioid, clear cell, mesonephric, serous, villoglandular and minimal deviation carcinoma are now defined. Adenosquamous carcinoma (5-25%), adenoid-cystic, adenoid-basal, neuroendocrine and undifferentiated carcinomas constitute other epithelia1 tumours of the cervix.

The management of invasive cervical carcinoma remains heavily dependent on its stage. The FIGO staging system remains the most widely used. The 1995 update provides more definite criteria in subdividing stage IA tumours by delimiting stromal invasion of stage IA1 lesions to a maximum depth of 3 mm and a horizontal axis of 7 mm.

In Malaysia, an appreciation of the cervical carcinoma problem has to take into consideration the population at risk, its multi-ethnicity, its socio-economic and geographical diversities and the constraints of the health care system. Females form 48.9% of the Malaysian population. 52.9% of them are in the sexually active age group of 15-50 years, indicating a significant population at risk for cervical carcinoma. Cervical carcinoma was the third most common cause of death due to solid tumours among Malaysian females in 1995 following carcinoma of the breast and respiratory tract. East Malaysia is predominantly rural with many communities having limited modern facilities. Such areas imply a lower educational and socio-economic status, raising the worry of a population at higher risk for developing cervical carcinoma. The population: doctor for Malaysia of 2153:1 compares poorly with nearby Singapore. Besides a shortage of doctors, there is also an uneven distribution of doctors, resulting in a ratio in East Malaysia of >4000:1. Although Malaysia does not have a national cervical cancer-screening programme, many action plans and cancer awareness campaigns have been launched throughout the years, which appear to have made an impact as evidenced by the decreasing mortality rates from cervical carcinoma. Another interesting feature of cervical carcinoma in Malaysia relates to its multiethnic population. In Malaysian Chinese and Malay females, the prevalence of cervical carcinoma ranks second to breast cancer whereas the pattern is reversed in Malaysian Indian females. Studies into its aetiology and pathogenesis are being undertaken and may shed more light on this matter.

Key words: Carcinoma cervix, Bethesda system, tumour staging, human papillomavirus, population statistics.

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HISTORICAL PERSPECTIVES

Worldwide, cervical carcinoma is second only to breast carcinoma in both incidence and mortality. More than 471,000 new cases are diagnosed each year, predominantly among the economically disadvantaged in both developing and industrialised nations.[1]

Since its recognition about 150 years ago,[2] there has been much progress in the understanding of the pathogenesis, prevention, early detection and management of cervical carcinoma. Important landmarks in the history of carcinoma of the uterine cervix are outlined in Table 1. Different aspects of the disease were concurrently studied and the most notable developments are summarized below.

1. Recognition of pre-invasive lesions and pre-clinical lesions

Important observations were made around the late 1800s and the turn of the 20th century that non-invasive precursor lesions preceded invasive squamous cell carcinomas of the cervix.[3] This ignited interest in the nomenclature, distinction and definition of the various grades of severity of the lesions. Broders popularised the term carcinoma-in-situ (CIS) in 1932[4] with Reagan introducing the concept of dysplasia in 1953.[5] Thenceforth, pre-invasive lesions were classified as dysplastic versus CIS. This was followed by Richart's cervical intraepithelial neoplasia (CIN) classification of pre-invasive lesions whereby CIS was considered part of the spectrum of CIN and not specifically distinguished from severe grade dysplasia as before.[6] Following on that, precursor lesions were classified as high or low grade squamous intraepithelial lesions at the National Cancer Institute Workshop in Bethesda in 1988.[7] This binary system of classification has however met with some resistance in its adoption as a uniform system for histological and cytological grading of precursor lesions and this issue is still being debated.

Apart from pre-invasive carcinoma, a pre-clinical, microscopically evident, microinvasive stage of cervical carcinoma, associated with decreased incidence of lymph node metastasis was described by Mestwerdt.[8]

2. Improvements in diagnostic techniques

Several technical advances developed through the years have made early detection hence treatment of cervical carcinoma a reality. One of the foremost developments is the "Pap" smear. Mooted by Papanicolaou in the late 1920s,

TABLE 1: Important dates in the history of carcinoma of the uterine cervix

Year	Events
1852	First description of invasive cervical carcinoma
1910	Recognition of non-invasive precursor lesions in cervical carcinoma
1925	Colposcopy first introduced
1928	Proposal of a cytological method to detect cervical cancer
1932	Carcinoma-in-situ (CIS) recognised
1934	Schiller stain proposed for detection of precursor lesions
1940s	Pap smear screening accepted
1951	Pre-clinical, microinvasive stage of cervical carcinoma first described
1953	"Dysplasia" introduced
1956	Description of koilocytic atypia
1968	Combination of CIS and dysplasia into CIN
1970 and 1980s	Use of electrocoagulation, cryotherapy and laser therapy for outpatient ablation of CIN lesions
1977	Association of koilocytosis with HPV
1983	Association of HPV 16 with CIS and invasive carcinoma
1988	Proposal of the Bethesda 2-tier classification system of precursor lesions
1989	Introduction of loop electrosurgical excision procedure (LEEP) for CIN lesions
1995	WHO International Agency for Research on Cancer concludes that there is compelling evidence to consider certain HPV carcinogenic
1996	National Institutes of Health Consensus Development concludes that cervical cancer is causally related with HPV

cytological examination of exfoliated cells obtained per *vaginum* became accepted as a mass screening technique for cervical cancers in the 1940s and "Pap smear screening" of women at risk is one of the major successes in the prevention of cervical cancer.[9-11] The colposcope also proved to be another important development. The colposcope, a stereoscopic binocular magnifying instrument, which macroscopically identifies cervical disease, was introduced by Hinselman in 1925.[12] In the 1930s, colposcopy gained wide acceptance in Europe for the identification of precursor lesions. Colposcopy is now an essential complementary technique in the evaluation of patients with abnormal cervical smears. Around 1934, Schiller described a method for detection of alterations in the cervical epithelium which suggested neoplastic transformation by an iodine reaction.[13] Schiller's Test is based on the normal production of glycogen by endocervical cells which stains dark blue on iodine application. Areas not exhibiting this blue staining would presumably be abnormal. This test unfortunately has some inherent pitfalls as some non-neoplastic conditions such as squamous metaplasia and cervicitis can give rise to a false positive Schiller's test. On the contrary, some neoplastic epithelium exhibit a false negative Schiller's test. Although lacking in specificity, the Schiller's test still has an adjunctive role in the determination of areas of the cervix for further study. Other diagnostic aids that were introduced and are still currently in use include the acetic acid test.[14] 5% acetic acid is normally used for the removal of mucus before colposcopic examination. Apart from removing mucus, acetic acid also dehydrates cells leaving areas of the cervix, with abnormal surface keratinisation, epithelial thickening or nuclear crowding, opaque and white thus aiding in the delineation of abnormal areas. As a result of these developments, current accepted triage for cervical malignancy should include exfoliative cytology, colposcopy and biopsy for confirmation of the nature of the lesion.

3. Therapeutic procedures

A major focus in the therapy of cervical malignancy has been in the development of outpatient procedures for precursor lesions, following the ability to detect early precursor lesions of cervical carcinoma. Various methods have been developed and used over time. Earlier methods concentrated on lesional ablation and these ranged from electrocoagulation, cryotherapy, laser therapy to infrared coagulation etc. The most popular among these techniques were electrocoagulation,[15,16] cryotherapy,[17,18] and C02 laser (light amplification by stimulated emission of radiation) therapy.[19,20] In recent years, the loop electrosurgical excision procedure (LEEP) under colposcopic guidance is fast gaining popularity over the orthodox surgical cone excision in preinvasive lesions of the cervix.[21,22] For invasive lesions, the mainstay of treatment still centres around surgery and radiotherapy. The value of chemotherapy is still being studied with cisplatin appearing to be the most promising agent with the best-documented response rate.'

4. Aetiopathogenesis

Another major breakthrough in cervical carcinoma was the recognition of the aetiological relationship between human papillomavirus (HPV) and cervical neoplasia. Since the first description of koilocytic atypia,[23] its association with HPV[24] and the recognition of HPV DNA in cervical carcinoma in 1983,[25] various epidemiological studies have supported this causal relationship.[26-32] The available epidemiological data has been recently reviewed by Munoz and Bosch and appears to fulfil the Bradford Hill criteria for causality.[33] This conclusion was endorsed by the World Health Organisation's International Agency for Research on Cancer (IARC) consensus panel in 1995 and the National Institutes of Health Consensus Development Conference in 1996.[1,34]

NORMAL ANATOMY AND PHYSIOLOGY OF THE CERVIX

An understanding of the normal anatomy and physiology of the cervix is important for proper understanding of the pathogenesis of neoplastic transformation in the cervix and will be briefly discussed.

The normal ectocervix, covered by non-keratinising stratified squamous epithelium, is continuous with the vaginal non-keratinised squamous epithelium below and the single layered, mucus-secreting, columnar epithelium of the endocervix above. In the native (original) state, the junction between the endocervical and ectocervical epithelium roughly corresponds with the external os. During the reproductive years, especially after the first pregnancy, the native squamo-columnar junction migrates outwards.

This results in a prolapse of endocervical epithelium covered cervix outside the external os. The single layered columnar epithelium makes for easy visualisation of the underlying stromal vessels giving rise to the historically misnomered "cervical erosion" in which there is no "erosion" of the covering epithelium but a physiological cervical ectopy or ectropion. In due course, the columnar epithelium is remodelled and replaced by metaplastic squamous epithelium. When this happens, there is a cephalad migration of the squamo-columnar junction again to create the "functional", in contrast with the "native", squamo-columnar junction. This results in the formation of a "transformation zone" i.e the area of the cervix between the original squamo-columnar junction (caudally located) and the new functional squamo-columnar junction (cephalically located). This is also the region originally covered by columnar epithelium and now covered by metaplastic squamous epithelium. In older females, the functional squamo-columnar junction migrates further up the endocervical canal.[35]

The transformation zone and development of pathology

The transforniation zone squamous epithelium is highly susceptible to malignant change. Virtually all neoplastic changes of the cervical epithelium originate at the functional squamo-columnar junction. The explanation for this is unclear but certain possible reasons have been put forward. Because of the low frequency of neoplastic transformation in areas of squamous epithelium detached from this region, it has been proposed that the endocervix plays a role in this phenomenon. The advancing edge of the cephalad-progressing squamous epithelium has been shown to be the least mature and this may influence its potential for malignant transformation. It has also been noted that when the squamous cells become neoplastic, they remain the least differentiated at the functional squamo-columnar junction compared with areas further from the junction. This may mean that the junction has some influence in the "maturation and differentiation" of the cells. It is feasible that the less mature and poorly differentiated cells possess a higher potential for mutational change. Another feature of the junctional region is its tendency to become inflamed and infected and this may also lead to alteration in its growth characteristics.[36]

It is important to note that the functional squamo-columnar junction retracts into the endocervical canal in older females. This results in cervical malignancy being more usually located in the ectocervical region in younger females and more in the endocervical canal in older women. Macroscopically, the ectocervical lesions tend to be exophytic and the endocervical ones endophytic. [37]

HISTOLOGICAL CLASSIFICATION OF CERVICAL CARCINOMA

The most frequently used histological classification system of cervical cancers is that proposed by the World Health Organisation (WHO). In existence for over 20 years, this classification system has been continually updated and the most recent update in 1994 (Table 2) was in collaboration with the International Society of Gynecological Pathologists.[38] Basically, cervical carcinoma is divided in the WHO Classification system into 3 main categories: squamous cell carcinoma, adenocarcinoma and other epithelia1 tumours. Pertinent histological features of each category are as follows:

1. Squamous cell carcinoma

Squamous cell carcinoma forms about 60-80% of invasive cervical carcinoma.[39] Due to the constant confusion in the previous WHO Classification between small cell non-keratinising squamous carcinoma and the small cell undifferentiated carcinoma with neuroendocrine features, the current classification merely divides the usual *invasive squamous cell carcinoma* into keratinising or non-keratinising variants. This dispenses with further subclassification of the non-keratinising variant by cell size. Apart from the usual squamous carcinoma, other types in the squamous category recognised in the current WHO Classification include verrucous, warty (condylomatous), papillary squamous (transitional) and lymphoepithelioma-like carcinoma. Formerly known as giant condyloma acuminatum of Buschke and Lowenstein, *verrucous carcinoma*, a slow growing and locally invasive malignancy is more commonly seen in the vulva but can be found in the cervix. Verrucous carcinoma must be differentiated from the *warty (condylomatous) carcinoma* which shows significant koilocytic atypia as well as features typical of the usual squamous cell carcinoma at the invasive edge. *Papillary*

TABLE 2: Modified World Health Organisation (WHO) Histological classification of carcinoma of the uterine cervix

Squamous cell carcinoma
Microinvasive squamous cell carcinoma
Invasive squamous cell carcinoma
Keratinising
Non-keratinising
Verrucous carcinoma
Warty (condylomatous) carcinoma
Papillary squamous cell (transitional) carcinoma
Lymphoepithelioma-like carcinoma
Adenocarcinoma
Mucinous adenocarcinoma
Endocervical type
Intestinal type
Signet ring type
Endometrioid adenocarcinoma
Endometrioid adenocarcinoma with squamous metaplasia
Clear cell adenocarcinoma
Minimal deviation adenocarcinoma
Endocervical type (adenoma malignum)
Endometrioid type
Serous adenocarcinoma
Mesonephric carcinoma
Well-differentiated villoglandular adenocarcinoma
Other epithelial tumours
Adenosquamous carcinoma
Glassy cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Adenoid basal carcinoma
Neuroendocrine carcinoma
Carcinoid-like tumour
Small cell carcinoma
Undifferentiated carcinoma

squamous (transitional) cell carcinoma is a rare type which histologically resembles urothelial transitional cell carcinoma. Nevertheless, there are focal areas of squamous differentiation and these tumours generally behave like the usual squamous cell carcinoma. The *lymphoepithelioma-like* carcinoma is a distinct subset of squamous cell carcinoma. These tumours resemble those found usually in the nasopharynx. Composed of syncitia of undifferentiated squamous cells, these tumours also have a prominent associated inflammatory infiltrate of lymphocytes, plasma cells and occasional eosinophils.

2. Adenocarcinoma

Adenocarcinoma constitutes about 5-15% of all invasive cervical carcinomas[40] with an increasing trend particularly in young females.[41,42] Like its squamous counterpart, preinvasive and microinvasive versions of adenocarcinoma are known. As in squamous lesions, preinvasive glandular dysplasia and in-situ adenocarcinoma are categorised together as cervical glandular intraepithelial neoplasia (CGIN). However, in contrast to CIN, criteria for grading CGIN are not as well established. This has led pathologists to advocate that until such criteria are well defined, preinvasive glandular lesions may best

be categorised as low or high grade CGIN. Like squamous carcinoma, adenocarcinoma of the cervix also arises at the functional squamo-columnar junction and involves the transformation zone of the cervix. It is noteworthy that almost 50% of invasive adenocarcinoma and 75% of in-situ variants are associated with CIN.[43,45] The similar site of origin and frequent association of glandular and squamous malignancies of the cervix suggest common aetiological factors in the pathogenesis of these tumours.

The 3 most common histological types of cervical adenocarcinoma are the rnucinous, endometrioid and clear cell types. In a study of 136 invasive adenocarcinoma of the cervix, the rnucinous type accounted for 57%, endometrioid 30%, clear cell 11%, and the other minor types together 2% of all the cases.[46]

Mucinous adenocarcinonza, the most common histological type of cervical adenocarcinoma, has **3** recognised variants. The endocervical variety shows glands lined by tumour cells which resemble the endocervical columnar epithelial cells with basal nuclei. Goblet cells, resembling those found in the large intestine are commonly found in the intestinal variant. Paneth as well as argentaffin cells are also noted at times in this variant. The third, signet ring carcinoma, displays signet ring cells, hence its name. *Endometrioid adenocarcinoma* is the second most common type of cervical adenocarcinorna. Histologically it resembles primary endometrial carcinoma, including the frequent finding of bland squamous clusters within the tumour. This makes it difficult at times to distinguish whether the cervical tumour is of primary origin or an extension of a tumour arising in the endometrium. Generally, it can be taken that most endometrial carcinomas would have invaded the myometrium and caused uterine enlargement by the time it involves the cervix, making a point for distinction. In contrast, the uterus is usually of a normal size in the case of primary cervical endometrioid carcinoma. *Clear cell adenocarcinoma* associated with in-utero diethyl-stilbesterol (DES) exposure usually occurs in younger patients while the sporadic cases are found in older women. Histologically, glycogen rich clear cells with occasional hobnailing are seen in solid, tubulo-cystic or papillary patterns in clear cell adenocarcinomas. *Minimal deviation adenocarcinoma (MDA)* is primarily diagnosed by observation of endocervical glandular penetration beyond the normal depth of extension, i.e. beyond two-thirds of the cervical thickness. The presence of occasional mitoses and haphazard gland arrangement, if present, also helps in the diagnosis. In MDA the malignant glands may be lined by cells resembling either endocervical (adenoma malignum) or endometrial epithelial cells (endometrioid variant). MDA has a known association with Peutz-Jegher's syndrome and ovarian mucinous and sex cord tumours with annular tubules.[47] *Serous adenocarcinoma* which histologically resembles its ovarian namesake, *mesonephric carcinoma* arising from the mesonephric duct remnant in the deep lateral wall of the cervix and *well-differentiated villoglandular adenocarcinoma* with long thin papillae are rare types of adenocarcinoma in the cervix.

3. Other epithelial tumours

Adenosquamous carcinoma constitutes between 5 to 25% of ail cervical carcinomas.[39] By definition, adenosquamous carcinoma should have malignant glandular and squamous components which are differentiated enough to be histologically recognisable. Glassy cell carcinoma is a rare, poorly differentiated variant of adenosquamous carcinoma with an extremely aggressive course. Mucoepidermoid carcinoma is another variant of adenosquamous carcinoma. The squamous component is usually of the non-keratinising large cell type in this tumour. Glands are usually absent, but intracytoplasmic mucin is produced by some tumour cells.

Adenoid cystic carcinoma, characterised by cylindrical hyaline bodies within nests of basaloid cells, and *adenoid basal cell carcinoma* made up of nests of cells with peripheral palisading resembling basal cell carcinoma of the skin are rare cervical tumours.

Neuroendocrine carcinoma is uncommon but a distinct entity in the cervix. Various degrees of neuroendocrine differentiation identified by conventional light microscopy, histochemical or immunohistochemical staining and electron microscopy are features of these tumours. They are thought to arise from the argyrophil cells of the cervix and are divided into carcinoid-like tumours and small cell carcinomas under the current WHO Classification. Carcinoid-like tumours are histologically similar to intestinal carcinoids. Usually well differentitated, they possess neurosecretory granules which may be immunopositive for a variety of hormones e.g. somatostatin, calcitonin, vasoactive intestinal polypeptide, antidiuretic hormone,

adrenocorticotropin hormone, gastrin etc. Unlike their intestinal counterparts, to date, there are no reports of these tumours being associated with the carcinoid syndrome. Small cell carcinoma, the other neuroendocrine carcinoma variant described in the WHO Classification, is histologically identical to the respiratory small cell carcinoma. These tumours can be difficult to differentiate from the non-keratinising squamous cell carcinoma with small cells. Immunohistochmeically, there is some overlap between the two tumours with 40% of non-keratinising squamous cell carcinoma with small cells exhibiting immunopositivity with synaptophysin, chromogranin or neuron-specific enolase and 40% of small cell carcinoma expressing cytokeratin. Nonetheless in general, small cell carcinoma presents around 40 years of age while the non-keratinising squamous cell carcinoma with small cells presents about a decade later.[48] Furthermore, like the oat cell carcinoma of the lung, small cell carcinoma in the cervix shows nuclearmolding which is almost never seen in non-keratinising squamous cell carcinoma with small cells. Another interesting feature of these tumours is that they are rarely associated with CIN change in the adjacent epithelium.[48,49] Instead, the possibility of a precursor lesion in the form of endocrine cell hyperplasia has been proposed.[50]

The WHO histological classification is useful in identifying various possible morphologies of cervical carcinoma. However, studies on differences in behaviour of the different histological types and variants of cervical carcinoma have generally produced controversial results. Except for a few tumours with recognisably more aggressive behaviour e.g glassy cell carcinoma,[51,52] adenoid cystic carcinoma,[53,54] and small cell carcinoma,[48,55] most other histological types do not show consistent differences.[56,57]

STAGING OF CARCINOMA OF THE CERVIX

By far, nodal status and staging still remain the most important factors that contribute to the prognosis of cervical carcinoma. The most widely used staging system of invasive cervical carcinoma is probably that of the Federation Internationale d'Obstetrique et Gynaecologie (FIGO). Throughout the years there have been several alterations in the FIGO staging of cervical cancers. In the current update (Table 3),[58] the most prominent changes from the 1988 version[5"] are essentially confined to stage I tumours. Basically, stage I refers to tumors limited within the cervix in contrast to extension outside the cervix i.e into the vagina, parametrium and pelvic wall. Extension into the corpus uteri is not taken into consideration and does not influence the staging of the tumour. Broadly, stage I tumours can be further subdivided into IA and IB. In concept, stage IA tumours imply microscopic tumours that are not detectable macroscopically. Although the FIGO Classification does not utilise the term "microinvasive carcinoma", it is generally accepted that FIGO stage IA tumours equate microinvasive tumours and these terms are used interchangeably in practice. In contrast, stage IB tumours can be grossly visible tumours that are confined to the cervix or microscopic tumours of dimensions larger than that defined for stage IA. Effectively, these broad concepts have been retained in the most recent classification, so has the further subdivision of stage IA into IA1 and IA2.

However, unlike the earlier classifications, the 1995 FIGO Classification provides for more definite criteria in subdividing stage IA lesions. In contrast to the earlier classification, the current one delimits stromal invasion of stage IA1 lesions to a maximum depth of 3 mm and a horizontal axis of 7 mm. This is instead of the former loose statement "minimal microscopically evident stromal invasion". The maximum depth and horizontal spread of stromal invasion of stage IA2 tumours remains unchanged in the current classification at 5 mm and 7 mm respectively. This would mean that stage IA2 in the new scheme would only include those tumours with depth of stromal invasion between 3 mm and 5 mm. This implies that some lesions previously staged as IA2 may now be IAI. The 1995 classification also further subdivides stage IB into IBI and IB2 for the first time. IBI lesions are defined as tumours less than 4 cm, and IB2, greater than 4 cm in diameter.

Essentially, management of patients with invasive cervical carcinoma is almost entirely dependent on the stage, underscoring the importance of the staging system. Since the introduction of the cut-off point for stage IAI tumours at 3 mm, there have been differing opinions regarding the appropriateness of this cut-off value. It has been noted that nodal metastases occurred in 0.2% of cases with tumours invading the stroma to a depth of <1 mm, 0.6% between 1 to 3 mm and 6.5% between

TABLE 3: The Federation of Gynecologists and Obstetricians (FIGO) staging for cervical cancer (1995)

Stage		
0		Carcinoma in situ, intraepithelial carcinoma. *Cases of Stage 0 should not be included in any therapeutic statistics for invasive carcinoma*
I		Carcinoma strictly confined to the cervix (extension to the corpus should be disregarded)
	A	Invasive carcinoma identified only microscopically. *All gross lesions, even with superficial invasion, are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm. (The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.)*
	A1	Measured invasion of stroma no greater than **3** mm in depth and no wider than 7 mm
	A2	Measured invasion of stroma greater than 3 mm but no greater than 5 mm in depth and no wider than 7 mm
	B	Clinical lesions confined to the cervix or **preclinical** lesions greater than IA
	B1	Clinical lesions no greater than 4 cm in size
	B2	Clinical lesions greater than 4 cm in size
II		The carcinoma extends beyond the cervix, but has not extended on the pelvic wall: the carcinoma involves the vagina, but not as far as the lower third
	A	No obvious parametrial involvement
	B	Obvious parametrial involvement
III		The carcinoma has extended on the pelvic wall; *on rectal examination there is no cancer-free space between the tumour and the pelvic wall;* the tumour involves the lower third of the vagina; *all cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to some other cause*
	A	No extension on to the pelvic wall, but involvement of the lower third of the vagina
	B	Extension on to the pelvic wall or hydronephrosis or nonfunctioning kidney
IV		The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and rectum
	A	Spread of the growth to adjacent organs
	B	Spread to distant organs

3 to 5 mm.[60,61] To some, these findings suggest a behavioural difference between tumours which invade the stroma up to a depth of 1 mm and those deeper. In addition, Burghadt ***et al*** showed that 1.4% of patients with lesions exhibiting stromal invasion of a depth between 1 to 3 mm died of the disease, a rate which did not differ significantly from 1.7% of cases with a stromal invasion depth between **3** to 5 mm. In contrast, the death rate was 6 times lower in patients with lesions which invaded the stroma to a depth less than 1 mm.[61] This has led to the contention that only lesions with stromal invasion up to 1 mm deserve to be considered separately. Other problems involved in using the FIGO staging system revolve around deciphering the "depth of invasion" of tumours, which is consequential in further assignment of stage IA tumours. Except for small cell carcinomas, stage IA is defined for the major histological types including squamous, adenosquamous and glandular carcinoma. Theoretically the depth of invasion should be measured from the base of the squamous or glandular epithelium at the point where invasion occurs. This requisite gives rise to appreciable difficulty especially in adenocarcinomas where the point of invasion is sometimes debatable.

PROBLEM OF CARCINOMA OF THE UTERINE CERVIX IN MALAYSIANS

Demographic profile of Malaysia

Malaysia, with a land area of about 329,733 square kilometres, is made up West Malaysia (Peninsular Malaysia) and East Malaysia (Sabah and Sarawak)[62] which differ in ethnic and socio-cultural profile.

The projected population of Malaysia in mid-1996 based on the 1991 population census was 21.2 million, of which Malaysians make up 93.4% and non-citizens 6.6%. About 80% of the total population resided in West Malaysia. Apart from being the more densely populated, West Malaysia was also the more urbanised with 54% of the population living in urban areas compared with 36% in East Malaysia. Females formed 48.9% of the total population with 52.9% of the female population between 15-50 years of age. Ethnically, Malaysians can be divided into three major groups. The Malays constituted 50.6%, Chinese 27.2% and Indians 7.7% of the total number of Malaysians. The other indigenous ethnic groups together made up 11.1% and other minority ethnic groups e.g. Eurasians etc. 3.4% of the total number of Malaysians. The Kadazans, Bajaus and Muruts of Sabah and the Ibans, Bidayuhs and Melanaus of Sarawak were among the largest indigenous ethnic groups which made up 11.1% of the total Malaysian population.

In 1991, there were 7198 doctors in Malaysia. 6544 (90.9%) were practising in Peninsular Malaysia, 298 (4.1%) in Sabah and 356 (4.9%) in Sarawak. The total population at this census was 17,563,420 with 14,131,723 (80.5%) in Peninsular Malaysia, 1,734,685 (9.9%) in Sabah, 1,642,771 (9.4%) in Sarawak and 54,241 (0.3%) in the Federal Territory of Labuan. The population per doctor ratio for the whole country was 2440 but this varied from 2168 in Peninsular Malaysia, to 5821 in Sabah and 4615 in Sarawak. This situation appeared to have improved slightly by 1995. The projected population in 1995 based on the 1991 census was 20,69 million. Assuming a similar distribution of population between West and East Malaysia, the estimated population of Peninsular Malaysia would have been 16,647,404, Sabah 2,043,488 and Sarawak 1,935,212. In the same year there were 9608 doctors in Malaysia. Of these, 8745 (91.0%) were stationed in Peninsular Malaysia and 407 (4.2%) Sabah and 456 (4.7%) Sarawak. Estimated population per doctor ratio would be 2153 for the whole country with 1904 in Peninsular Malaysia, 5021 Sabah and 4244 Sarawak. With regards to health care facilities, there were 75 hospitals and 4 special medical institutions run by the government in West Malaysia which provided a total capacity of 27,273 beds in 1995. Sabah had 17 hospitals and 1 special medical institution with a total of 3009 beds while Sarawak had 19 hospitals and 2 special medical institutions with a total of 3306 beds. This data did not take into account private medical institutions, the majority of which are located in West Malaysia.

Carcinoma of the Uterine Cervix in Malaysian women and in the female population of neighbouring Singapore

Malaysia

Carcinoma of the uterine cervix is one of the most common cancers and is among the leading cause of death from solid tumours in Malaysian women. It accounted for 142 medically certified deaths in Malaysian women in 1995 i.e. 1.43 deaths per 100,000 women. It was only behind carcinoma of the breast with 320 deaths (3.23 per 100,000 women) and cancers of the respiratory system which resulted in 254 deaths (2.56 per 100,000 women).[63] Information on the incidence and prevalence of the disease is not readily available but local studies have indicated that carcinoma of the uterine cervix together with carcinoma of the breast are the two foremost malignancies in Malaysian females. This pattern appears to hold for both East and West Malaysia.[64-67]

Of the 142 deaths from cervical carcinoma in 1995, all deaths occurred after 29 years of age with the largest number occurring in the 45-49 years age group.[63] A study which analysed data from 7 hospitals in Penang between 1987-1990 showed that carcinoma of the cervix was the second most common malignancy among Chinese and Malay females. In this study, it was shown that breast carcinoma was the leading cancer reported among the females of these two ethnic groups. In contrast, cervical carcinoma was the most frequent carcinoma reported among the Indians while breast carcinoma was second.[67]

Singapore

Historically one of the states of Malaysia, the island republic of Singapore, which lies south of Peninsular Malaysia, shares certain similarities with Malaysia. Understanding of cervical carcinoma in Malaysians would seem incomplete

without some understanding of the problem in Singapore.

Singapore's total population at the 1990 census was 3,016,379 with a resident (citizens and permanent residents) population of 2,705,115.[68] Chinese formed 77.7%, Malays 14.1%, Indians 7.1% and other minority ethnic groups 1.1% of the total resident population. In 1992, Singapore had 3798 doctors and the population per doctor ratio stood at 711.[69] Cervical cancer was reported as the second most frequently encountered cancer in Singaporean females during the 5-year period between 1968-1972, following behind breast cancers. In the next 5 years, between 1973-1977, it was superseded by colorectal cancers and became the third most common cancer. Subsequently between 1978-1982, it had dropped to being the fourth most common cancer behind breast cancer, colorectal cancer and lung cancer in that rank order. This pattern has since remained up to 1992. The age-standardised incidence rate of cervical cancer in Singaporean females between 1988-1992 was 15.2/ 100,000/year. However, although it was the fourth most common cancer among the ethnic Chinese and Malay Singaporeans, cervical cancer was the second most common malignancy among the ethnic Indian Singaporean females, after breast cancer.

For a wider perspective, Table 4 summarises a comparison of age-standardised incidence rates of cervical cancer from several other countries.

TABLE 4: International comparisons of age-standardised incidence rates of cervical cancer between 1983-1987[69]

Country/City	Age standardised incidence rate (/100,000/year)
Columbia, Cali	42.2
US, Los Angeles	
White	7.2
Black	12.2
Chinese	12.3
US, Connecticut	
White	6.9
Black	13.0
Denmark	15.9
UK, Birmingham	13.9
Australia, NSW	11.0
New Zealand	
Maori	29.9
Non-Maori	11.8
Hawaii	
Hawaiian	10.1
Chinese	3.8
Japan, Osaka	13.2
China, Shanghai	4.3
Hong Kong	19.2
India, Madras	47.2
Singapore	
Chinese	17.5
Malay	8.8
Indian	12.7

DISCUSSION

Carcinoma of the uterine cervix has come a long way since its recognition 150 years ago. Improvements in the understanding of the aetiology, pathogenesis and disease course, diagnostic techniques and treatment modalities have served to decrease the incidence, morbidity and mortality of the disease over time.

It is important to highlight certain aspects of the make-up of Malaysia to provide a better understanding of the problem of cervical carcinoma in Malaysian women.

1. Population at risk

In the latest population statistics publication, females formed almost half (48.9%) of the total population. More importantly, more than half (52.9%) of the female population were in the sexually active age group, i.e. between 15-50 years of age, also the group most prone to cervical carcinoma. It is easily recognisable from these figures that there is a significant Malaysian female population at risk for cervical carcinoma.

Apart from identifying a significant population at risk for cervical carcinoma, examination of the statistical data confirms that Malaysian women are not spared from this disease. Cervical carcinoma was the third most common cause of death due to solid tumours among Malaysian females in 1995 following carcinoma of the breast and carcinomas of the respiratory tract (trachea, bronchus and lung) in that rank order. From the few Malaysian studies available on cancer incidence, it appears that cervical carcinoma is the second most common

malignancy in females after carcinoma of the breast. Taking into consideration the highly aggressive and poor therapy amenable nature of cancers arising from the respiratory system which obviously contributes to its high mortality rate, the mortality statistics also support the possibility of cervical carcinoma being the second most frequent malignancy in Malaysian females.

2. Diversity of the Country

West Malaysia, the more urbanised and densely populated part of the country is diverse in terrain as well as distribution, ethnic composition, primary occupation, etc of the population throughout the 11 constituent states and the Federal Territory of Kuala Lumpur. These differences become even more palpable when compared with East Malaysia, which is separated from the peninsula by 540 kilometres of sea. With 20% of the total Malaysian population living in a land area (124,449 square kilometres) not very much smaller than West Malaysia (131,573 square kilometres), East Malaysia is less densely populated. In comparison with West Malaysia, 64% of East Malaysian population was rural whereas more than half of West Malaysia (54%) was urban during the 1991 census. Apart from being predominantly rural, it is also important to understand that many East Malaysian communities live in fairly inaccessible areas with limited availability of modem facilities. Rural, inaccessible areas usually imply a lower educational and socio-economic status in Malaysia. This raises the worry of a fairly large Malaysian population, which could be at a higher risk for developing cervical carcinoma. At the same time, this has to be weighed against the known fact that rural populations tend to be less sexually promiscuous.

3. Distribution of health care

Even though the population served per doctor for the whole country appears to have improved from 2440 (2168 in Peninsular Malaysia, 5821 Sabah, 4615 Sarawak) in 1991 to 2153 (1904 in Peninsular Malaysia, 5021 Sabah and 4244 Sarawak) in 1995, there is still a vast shortage of doctors. This is evident when compared with neighbouring Singapore which recorded 711 population per doctor in 1992. Besides the general shortage, the other striking problem appears to be the uneven distribution of doctors. There was negligible alteration in the situation from 1991 to 1995. In both years, about 91% of the total number of doctors in the country served 80% of the population residing in West Malaysia. Only 9% of the total number of doctors serviced the remaining 20% of the population residing in East Malaysia. Unlike the distribution of doctors, the number of government hospital beds were more appropriately distributed between East and West Malaysia. In 1995, 81% of the total number of hospital beds in the country catered to the needs of 80% of the total population in West Malaysia. Along the same line, 19% of the total number of government hospital beds catered to 20% of the total population in East Malaysia. This reiterates the observation that governmental attempts to ensure an even distribution of health care facilities are often frustrated by the general reluctance of doctors to service the less developed Eastern part of the country.

Taking these factors into consideration, it is quite clear that cervical carcinoma is an important problem in Malaysia. Most effective combative measures for this disease have always been primarily dependent on early detection and treatment of precursor lesions. This is obvious when note is made that most countries with low incidence of cervical carcinoma, e.g. United Kingdom (Table 4), have some form of cervical cancer screening programme. Success of these programmes is always contingent on its reach. Malaysia, due to its diversity of terrain, which is quite inaccessible at times, and limited medical facilities, still faces difficulties in the implementation of extensively reaching health programmes. There is also a lack of accurate medical documentation which hinders proper health planning. This shortfall is evidenced by the fact that in 1995, only 44% of the total deaths in Malaysia were medically certified. The larger proportion had not been examined by any medical practitioner. The low number of medically certified deaths provides an indication of even more pronounced difficulties in compilation of disease incidence data, which has no legal obligation for notification compared with mortality.

At this juncture it is noteworthy that given the logistic problems in Malaysia in the implementation of certain health measures, data (Table 5) on death rates from breast and cervical carcinoma between 1988 and 1992 show an interesting trend.[70] The projected mid-year population of 1988 was 16,941.8 million, with females making up 8,405.1 million, while that in 1992 was 18,615.4 with 9231.0 million females.[71,72] This shows a 9.8% increase in the female population between 1988 to 1992. The

TABLE 5: Number of medically certified cases of death in breast and cervical cancers in Malaysian females in the 5 year period between 1988-1992.[70]

No. of deaths	Year				
	1988	1989	1990	1991	1992
Breast cancer	172	202	246	251	246
Cervical cancer	141	112	136	132	125

number of deaths from breast carcinoma increased from 172 to 246 (43.0% increase) while deaths from cervical carcinoma recorded a decrease from 141 to 125 (11.3% decrease) between this same period. It appears that deaths from breast carcinoma increased disproportionately to the natural increase of the female Malaysian population while deaths from cervical carcinoma had decreased.

This decline of cervical carcinoma is also evident in Singapore where the age-standardised incidence rate of cervical carcinoma has continuously decreased from 18.1 between 1968-1972, to 17.5 between 1973-1977, 16.6 between 1978-1982, 16.1 between 1983-1987 to 15.2 per 100,000 per year between 1988-1992.[69] Cervical cancer has also declined from being the second most common cancer in Singaporean females between 1968-1972, to the third position between 1973-1977 and the fourth between 1978-1992. This decline in ranking of cervical carcinoma was related both to a decrease in incidence of this disease as well as an increase in the other carcinomas like breast, colorectal and lung in the female Singaporean population.

Although Malaysia has not been able to institute a national cervical cancer-screening programme to date, many cancer awareness campaigns among the public have been launched throughout the years. Women at risk have been encouraged to partake in voluntary cervical cancer screening schemes which have become more popular with time, increased public awareness and improved socio-economic and educational status. Although it is unquestionable that a National Cervical Cancer Screening Programme is essential to lower the cervical cancer rates further, it is clear that the *adhoc* measures have made some impact as evidenced by the decreasing mortality rates.

Another interesting feature of cervical carcinoma in Malaysia and Singapore is dictated by the multi-ethnic composition of the population of both countries where the three main ethnic groups are Malays, Chinese and Indians. In the Malaysian study (1987-1990) by Chan *et al*, breast carcinoma was the most common malignancy among the Chinese and Malay females and this was followed by cervical carcinoma. This pattern was reversed among the Malaysian Indian females with cervical carcinoma being the most frequent malignancy followed by breast carcinoma.[67] Around the same period (1988-1992) breast carcinoma was also the most frequent malignancy among the women of all three major ethnic groups in Singapore. In comparison, cervical carcinoma ranked as the fourth most common malignancy among the Chinese and Malays, while it was the second among ethnic Indian Singaporean women.[69] The age-standardised incidence rates from the two sources showed an inconsistent pattern (Fig. 1). Taken together, it would appear that the Chinese in Malaysia and Singapore had roughly similar age-standardised incidence rates of cervical carcinoma. The Malays in Malaysia showed a lower age-standardised incidence rate compared with Singaporean Malays. The Malaysian Indians demonstrated a high age-standardised incidence of cervical carcinoma compared to their Singapore counterparts. The combined data seem to indicate that carcinoma of the cervix is a prominent disease among Indian females. Cervical carcinoma was more common than breast carcinoma among the Malaysian Indian, and more common than the three other carcinomas emerging in the other two ethnic groups i.e. colorectal, lung and ovarian carcinoma among Singaporean Indian women. The high incidence of cervical carcinoma among Malaysian Indian compared with Singaporean Indian females requires further clarification. It is doubtful that the lower incidence in Singapore was mainly due to under-reporting, a problem which would seemingly have been less in the island republic than Malaysia. Although the reasons for this finding remains unclear, it does suggest that environmental influences are probably more important than genetic ones in development of cervical carcinoma. The reason for the lower incidence of cervical carcinoma among Malaysian compared with Singapore Malays is also unclear. Whether this is the result of under-reporting among this ethnic community in Malaysia or a true representation of higher incidence of cervical carcinoma among Malays residing in Singapore requires further investigation.

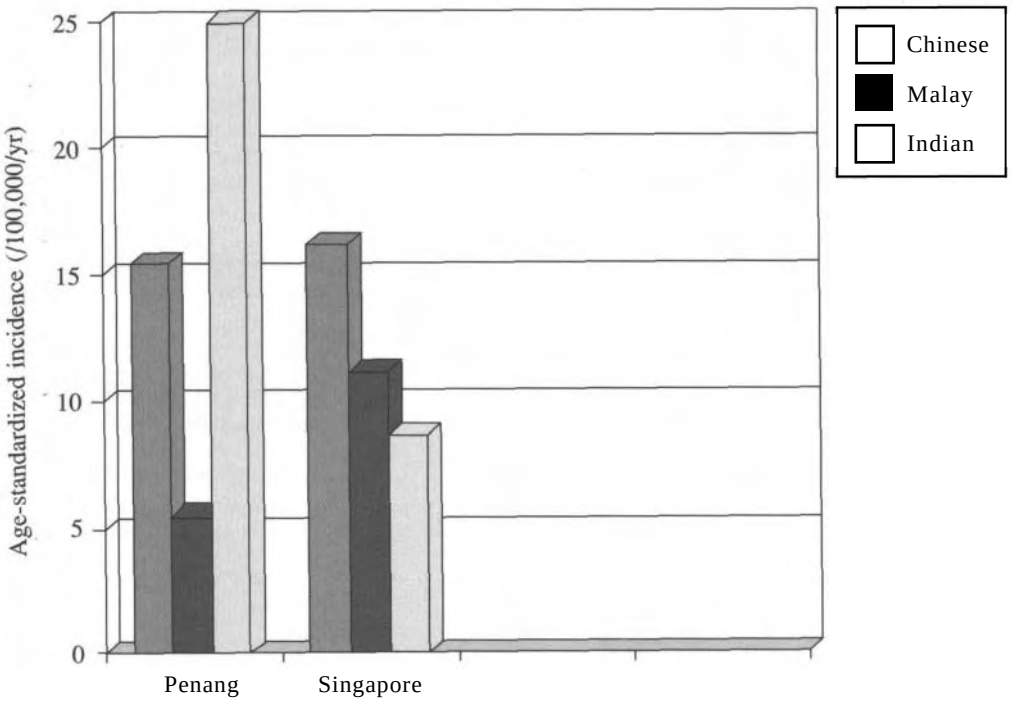

FIG. 1: Age standardised incidence rate of cervical cancer in Penang (1987-1990) compared with Singapore (1988-1992) for the 3 major ethnic groups.

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