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**EPIDEMIOLOGY AND SEROLOGY OF GYNAECOLOGICAL NEOPLASMS
IN MALAYSIA**

A Dissertation Submitted to the University of Malaya in Partial Fulfilment of the
Degree of Master of Philosophy

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ABSTRACT

A total of 789 cases of gynaecological neoplasms were recorded during the nine-year period from 1985 to 1993 at the Radiotherapy Unit, General Hospital Kuching, Sarawak, Malaysia. In the present study, the patterns and frequencies of four different sites of gynaecological neoplasms, namely, cervix, ovary, endometrium and vulva/vagina were analysed in the various age and ethnic groups. The highest frequency of gynaecological neoplasms occurred among the Chinese (42.6 %) followed by the Ibans (21.9%), the Malays (19.4%) and the other Indigenous Groups (15.2%). All ethnic groups except the Indigenous Groups showed similar pattern of gynaecological neoplasms. The leading cancer site is the cervix, followed by the endometrium, the ovary and vulva/vagina. Among the Indigenous Groups, ovarian cancer comes second after the cervix. The age distribution of the patients showed an increasing number of patients with increasing age and all gynaecological neoplasms were predominant in age groups above 40 years. However, among patients below the age of 40 years, endometrial cancer showed a higher percentage compared to the others. The age standardised rate (ASR) for cervical cancer in Sarawak was 9.9. The Chinese (15.5) and the Ibans (10.7) appeared to have much higher ASR than the Malays (6.3) and the other Indigenous groups (5.4).

The increased risk of cervical neoplasia with seropositivity against multiple viral infections has been reported in several studies. In the present study, the seroepidemiological association of human papillomavirus (HPV), human herpes

simplex virus II (HSV-II), human cytomegalovirus (CMV), Epstein-Barr virus (EBV) and carcinoma of the cervix were performed. Sera from 69 cases of cervical cancer attending the Gynaecology Clinic, Hospital Kuala Lumpur and sera from 44 normal pregnant women attending the Antenatal Clinic, Hospital Kuala Lumpur were screened for HPV, HSV-II, CMV and EBV antibodies. The IgG, IgA and IgM antibodies were measured against HPV type 16 using the enzyme-linked immunosorbent assay (ELISA). For CMV and HSV-II, only the IgG antibodies were measured using ELISA. The IgG and IgA antibodies against EBV viral capsid antigen (VCA) and IgG against EBV early antigen (EA) were measured using the immunofluorescence assay. For the antibodies against HPV 16 E7 protein, cervical carcinoma cases were 23.2% IgG positive, 27.5% IgA positive, 13.0% IgG and IgA positive, and 56.5% IgM positive. The normal pregnant women showed similar pattern where 15.6% were IgG positive, 15.6% IgA positive, 3.0% IgG and IgA positive, and 62.5% IgM positive. Both cervical carcinoma patients and normal pregnant women showed a very high prevalence of IgG antibody to HSV-II i.e. 95.6% and 84.0% respectively. The IgG antibody prevalence to EBV-VCA were also found to be very high in cervical carcinoma cases (88.4%) and normal pregnant women (95.4%). The IgG antibody prevalence to CMV was found to be higher in cervical carcinoma cases (98.6%) than in normal pregnant women (20.4%). In the assessment of antibody prevalence according to their HPV seropositive and seronegative status, both cervical cancer patients and normal pregnant women have high prevalence of HSV-2 and CMV infection regardless of their HPV seropositivity status. However, the prevalence for the various EBV-associated antibodies among HPV seropositive cervical carcinoma

cases were higher compared to HPV seronegative cases. From the results obtained, there seemed to be no correlation between HSV-II or CMV infection and HPV positivity, but there seemed to be a positive correlation between EBV infection and HPV infection. The results obtained suggest that EBV in association with HPV may play a role in the carcinogenesis of cervical cancer.

ABSTRAK

Sebanyak 789 kes neoplasma ginekologi telah direkodkan di Unit Radioterapi, Hospital Umum Kuching, Sarawak dalam jangka masa 9 tahun iaitu dari tahun 1985 hingga 1993. Penyelidikan ini mengkaji pola dan frekuensi 4 neoplasma ginekologi iaitu serviks, ovari, endometrium dan vulva/vagina dalam pelbagai kumpulan etnik dan usia. Kumpulan etnik Cina menunjukkan frekuensi neoplasma ginekologi tertinggi (42.6%) diikuti oleh kaum Iban (21.9%), Melayu (19.4%) dan kaum Peribumi yang lain (15.2%). Kesemua kumpulan etnik kecuali Kaum Peribumi selain Iban mempunyai corak neoplasma ginekologi yang serupa. Barah serviks didapati sebagai barah paling utama diikuti oleh barah endometrium, barah ovari dan vulva/vagina. Di kalangan Kumpulan Peribumi selain Iban, barah ovari menduduki tempat kedua diikuti oleh barah endometrium. Secara amnya, taburan usia pesakit menunjukkan peningkatan bilangan pesakit dengan peningkatan usia. Kesemua neoplasma ginekologi didapati lebih dominan dalam kumpulan-kumpulan umur melebihi 40 tahun. Namun demikian, di kalangan pesakit yang berusia di bawah 40 tahun, barah endometrium menunjukkan peratus yang lebih tinggi berbanding barah-barah lain. Kadar umur piawai bagi barah serviks di Sarawak ialah 9.9. Kumpulan etnik Cina (15.5) dan Iban (10.7) menunjukkan kadar umur piawai yang lebih tinggi berbanding Melayu (6.3) dan kaum Peribumi lain (5.4).

Banyak kajian yang telah melaporkan peningkatan risiko barah serviks dengan seropositiviti terhadap jangkitan virus berbilang. Dalam penyelidikan ini, satu kajian

hubungan seroepidemiologi karsinoma serviks dengan virus papilloma manusia (HPV), virus herpes simplex manusia jenis II (HSV-II), 'cytomegalovirus' manusia (CMV) dan virus Epstein- Barr (EBV) telah dijalankan. Penyaringan antibodi-antibodi terhadap HPV, HSV-II, CMV dan EBV telah dilakukan ke atas 69 sampel serum daripada pesakit karsinoma serviks yang mengunjungi Klinik Ginekologi, Hospital Kuala Lumpur dan 44 contoh serum daripada wanita normal yang hamil yang mengunjungi Klinik Antenatal, Hospital Kuala Lumpur. Antibodi IgG, IgA dan IgM terhadap HPV-16 disukat menggunakan ELISA, manakala bagi CMV dan HSV-II hanya antibodi IgG sahaja yang disukat menggunakan ELISA. Antibodi IgG dan IgA terhadap EBV-VCA dan antibodi IgG terhadap EBV-EA disukat menggunakan kaedah cerakan imunofluoresen. Bagi antibodi-antibodi terhadap protein HPV 16 E7, di kalangan pesakit karsinoma serviks, didapati 23.2% adalah positif terhadap IgG, 27.5% positif terhadap IgA, 13.0% positif terhadap IgG dan IgA, dan 56.5% positif terhadap IgM. Bagi wanita hamil, pola yang sama juga ditunjukkan iaitu 15.6% adalah positif terhadap IgG, 15.6% juga positif terhadap IgA, 3.0% positif terhadap IgG dan IgA, dan 62.5% positif terhadap IgM. Pesakit karsinoma serviks dan wanita hamil menunjukkan prevalens antibodi IgG yang tinggi terhadap HSV-II iaitu 95.6% dan 84.0% masing-masing. Prevalens antibodi IgG yang tinggi terhadap EBV-VCA juga ditunjukkan oleh pesakit karsinoma serviks (88.4%) dan wanita hamil (95.4%). Prevalens antibodi IgG terhadap CMV di kalangan pesakit karsinoma serviks (98.6%) adalah lebih tinggi daripada wanita hamil (20.4%). Pesakit karsinoma serviks dan wanita hamil yang normal juga menunjukkan prevalens antibodi yang tinggi terhadap jangkitan HSV-II dan CMV tidak kira sama ada ia seropositif atau seronegatif

terhadap HPV. Namun demikian, pesakit karsinoma serviks yang seropositif terhadap HPV menunjukkan prevalens yang tinggi terhadap pelbagai antibodi-antibodi EBV berbanding pesakit yang seronegatif terhadap HPV. Dari hasil penyelidikan ini, tiada kemungkinan terdapatnya kaitan di antara jangkitan HSV-II atau CMV dengan positiviti HPV, tetapi ada kemungkinan EBV mempunyai kaitan dengan jangkitan HPV. Hasil penyelidikan yang didapati mengesyorkan bahawa EBV bersama HPV mungkin memainkan peranan dalam karsinogenesis barah serviks.

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LIST OF ABBREVIATIONS

%	percentage
°C	degree centigrade
μ	micron
μg	microgramme
μl	microlitre
AP	alkaline phosphatase
ASR	age standardized rate
BL	Burkitt's lymphoma
BSO	bilateral salphingo-oophorectomy
CIN	cervical intrepithelial neoplasm
CMV	cytomegalovirus
CO ₂	carbon dioxide
CT	computed tomography
D & C	dilatation & curettage
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
EA	early antigen
EBNA	Epstein-Barr virus nuclear antigen
EBV	Epstein-Barr virus
ELISA	enzyme-linked immunosorbent assay

FCS	foetal calf serum
FIGO	International Federation of Gynaecology and Obstetrics
g	gramme
GMT	geometric mean titre
h	hour
HD	Hodgkin's disease
HKL	Hospital Kuala Lumpur.
HPV	human papillomavirus
HRT	hormon replacement therapy
HSV	herpes simplex virus
IE	immediate early
LCL	lymphoblastoid cell lines
LMP	latent membrane protein
LOH	loss of heterozygosity
LS	lamb serum
min	minute
ml	millilitre
ng	nanogramme
nm	nanometre
NaOH	sodium hydroxide
NPC	nasopharyngeal carcinoma
ORF	open reading frame

PAC	cisplatin Andriamycin-cyclophosphomide
PBS	phosphate buffered saline
PBS-T	phosphate buffered saline-tween
rpm	revolution per minute
RT	room temperature
SHBG	sex hormone binding globulin
TAH	total abdominal hysterectomy
TPA	12-0-tetradecanoyl phorbol-13-acetate
TSG	tumour suppressor gene
VCA	viral capsid antigen

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