CHAPTER 5 : DISCUSSION

5.1 EPIDEMIOLOGY OF GYNAECOLOGICAL NEOPLASMS IN SARAWAK FEMALES

In the present study, cervix neoplasia was found to be the most frequent gynaecological neoplasms among all females of different ethnic races in Sarawak. It formed the majority of cases which accounts for about 85.4 per cent cases reported from the years 1985 to 1993 at the Radiotherapy Unit, General Hospital, Kuching, Sarawak. Carcinoma of the endometrium, ovary and vulva and vagina formed the remaining proportion of gynaecological neoplasms among Sarawak females.

All ethnic races, namely the Chinese, Malays and Indigenous Groups (which include the Iban and other Indigenous groups) showed similar pattern of gynaecological neoplasms where the most frequent cancer site was the cervix, followed by the endometrium, the ovary and vulva and vagina. Except in the Indigenous Groups, ovarian cancer comes second after the cervix.

The general age pattern of most gynaecological cancers analysed showed an increasing number of patients with increasing age. Majority of all gynaecological neoplasms patients were found to be above the age of 40 years. One suprising finding was that the percentage of endometrial cancer cases which were below the age of 40 years appeared to be higher than the other gynaecological neoplasms cases (about two fifth of all endometrial cancer cases). Endometrial cancer has been known to be

primarily found in postmenopausal women between the age of 50 and 60 years. The disease was also pronounced among obese women. The association between endometrial cancer and body weight in Sarawak females however has never been studied.

Cervix neoplasm

In the present study, it is observed that cervix neoplasm formed the majority of all gynaecological neoplasm among all females of different ethnic races in Sarawak. The Chinese and the Indigenous groups showed almost equal percentage of cervix neoplasm patients, which is double of the Malays. The peak incidence is in the 41 - 50 years age group. This is comparable to the study carried out in Sabah where cervical cancer was found to be the most frequent gynaecological cancer among the Chinese, followed by the Indigenous Groups and the Malays (Ganesan *et. al.*, 1991). A study carried out in West Malaysia also demonstrated a high incidence of cervical cancer among the Chinese, followed by the Indians and the Malays (Azhar and Lopez, 1989). The age standardized rate (ASR) calculated for cervical cancer in Sarawak is 9.9 and is lower than the ASR for the northern population of West Malaysia recorded in the Penang Cancer Registry (1996) i.e. 15.03. The ASR for cervical cancer in Malaysia for the year 1985 recorded in the IARC *Incidence of Cancer* (1998) is 12.2.

In the overall Malaysian population, cervical cancer has been shown to be the most frequent gynaecological cancer with a peak incidence of 50 -54 years age group. It is

the most frequent cancer for the Chinese and Indian females and the second most frequent cancer for the Malay females after breast cancer (Norhanom and Yadav, 1995). In Brunei, the Chinese were found to have a higher rate of cervical cancer as compared to the Malay females (Affandi *et al.*, 1993). Singapore also had cervical carcinoma rate which is more than half of Malaysia, even lower than the rate of cervical carcinoma in the United States. The Indians in Singapore were shown to have the highest rate of cervical cancer i.e. 50 per cent higher than the Chinese and almost 3 times that in Malays (Lee *et al.*, 1988). This is expected since the Indians of Singapore were mostly migrants from India where cervical cancer is reported to be common among Indian females. Cancer of the cervix is about twice as common in Asia as in Europe and North America. It is the most common gynaecological cancer in developing countries and the second common cancer in women worldwide after cancer of the breast (Parkin, 1992). In developed countries except United States, carcinoma of the cervix is the leading genital cancer followed by the ovary and the uterus. In the United States, cervical cancer ranked third after cancer of the uterus and ovary (IARC *Incidence of Cancer*, 1998).

In western countries, early age at first intercourse, multiple sexual partners and infection with HPV are major risk factors for cervical cancer. In Hong Kong, Taiwan and Singapore, multiple sex partners, infections with HPV and HSV-2, poor personal hygiene, and cervicitis have been reported as the risk factors for the Chinese living in these countries (Lim-Tan *et al.*, 1988 ; Donnan *et al.*, 1989 ; Peng *et al.*, 1991). In Singapore, parity and number of sex partners were found to be the most important risk

factors for cervical cancer and education lowered the risks. However, infection with HPV were lower than in many Western series (Cuzick *et al.*, 1989). Low prevalence of HPV infection in cervical carcinoma was also reported in Brunei (Affandi *et al.*, 1993). The lower prevalence of HPV infections in regions of high incidences of cervical neoplasm merits further studies.

Apart from the risk factors stated above, the relatively higher incidence of cervical cancer among the Chinese as seen in the present study may be attributed to the better reception of the Chinese to modern medicine compared to others who were reluctant to seek medical treatment because of the cancer stigma and related prejudice (Azhar and Lopez , 1989). Other factor may be attributed to the higher utilisation of hospitals by the Chinese since the Chinese normally live in urban areas (Thanaletchumy and Thangam, 1988).

In the present study, the incidence of cervical cancer among the Indigenous Groups of Sarawak were found to be almost as high as the Chinese. This is comparable to other epidemiological studies which showed that the highest rates of cervical cancer are generally observed in indigenous or long-term resident migrant minority groups. The incidence rates for Hispanics and American Indians were approximately double those of whites (Polednak, 1993) and the rates among blacks in US were about twice as high as those among whites (Brinton and Fraumeni, 1986). In general, the Indigenous Groups of Sarawak are of lower socioeconomic status and live in rural areas. Looking at the population percentage of the Indigenous Groups of

Sarawak which is double of the Chinese, there may be underreporting of the number of cases recorded. This may be attributed to the distance from the hospitals and remoteness of their homes. The association of low socioeconomic status with cervical cancer rates is well established. Women of low socioeconomic status usually with low educational level were often affected by cervical cancer. Education is important in relation to the knowledge of cervical cancer screening and sexual behaviour determinants.

The incidence of cervical cancer among Malay females in the present and other studies have been reported to be low compared to the Chinese and Indigenous Groups. Although the Malays marry at an earlier age and bore many children they showed low rates of cervical cancer (Affandi *et al.*, 1993). This may be because they belong to the Orthodox Muslim Society which do not tolerate multiple partners. Population studies have shown that the rate of cervical cancer among Muslims and Jews in the Middle East is lower than in the West. This has been attributed to the religious practice of circumcision of the Muslim males (Kjaer *et al.*, 1991).

Ovarian neoplasm

The incidence of ovarian neoplasm in the present study showed similar racial pattern compared to cervical neoplasm. The Chinese is still the leading ethnic race followed by the Indigenous Groups and the Malays. The peak incidence is in the age group 41 - 50 years and is comparable to the report by Barber (1993) and Norhanom

and Yadav (1995). The ASR for ovarian cancer in Sarawak was not analyzed due to the small sample of the study population. The Penang Cancer Registry (1996) reported the ASR for ovarian cancer for the northern region of West Malaysia is 4.09 and is comparable to the ASR for 1985 recorded in the IARC *Incidence of Cancer,* 1998 i.e. 4.8.

Ovarian disease were seen more frequently in developed countries like Japan, United States and Australia and the incidence has remained stable over the last 20 years (Tomatis *et al.,* 1990). In the IARC *Incidence of Cancer,* 1998, the incidence of ovarian cancer in Singapore and Malaysia were shown to have increased substantially. The incidences in other Asian countries were about half of the incidences in developed countries.

Reproductive and hormonal effects have been shown to be associated with ovarian neoplasm. The only established (protective) risk factors for ovarian cancer are parity and use of oral contraceptives (Negri *et al.*, 1991; Franceschi *et al.*, 1991; Whittemore *et al.*, 1992a). The risk of ovarian neoplasm decreased with increasing number of pregnancies. This may partly explain the low incidence of ovarian neoplasm among the Malay females who are known to bear many children but did not explain the higher incidence in Indigenous Groups who also bore many children. In most European studies, late age at menopause has been shown to increase the risk for ovarian cancer (Franceschi et. al., 1991) but not in most American investigations (Whittemore *et al.*, 1992b). The widespread use of menopausal estrogens among American women may

partly explain this discrepancy. Most previous studies found no evidence that late age at menarche represents a risk factor for the disease except one study on a Chinese population in China (Shu *et al.*, 1989). Based on this fact, it is necessary to carry out similar studies on the Chinese in Malaysia to derive any possible association.

The risk of ovarian neoplasm had also been associated with family history of the disease. Increased risk had also been shown in women with a family history of colorectal, breast or uterine cancer. The existence of a breast-ovarian cancer syndrom may result from the pleiotropic effects of the same gene in some families. Mutations in BRCA1 and BRCA2 in women with breast cancer have been associated with an increased risk of ovarian cancer (Langston and Ostrander, 1997). Three to eight per cent of all women with breast cancer were found to carry a mutation in one of these genes (Brody and Biesecker, 1998). Analysis of these genes should be considered for women diagnosed with breast cancer. Molecular genetic changes which involved a high frequency of allelic loss of the p53 gene has also been implicated (Tsao, 1991). Somatic allelic deletion or loss of heterozygosity (LOH) has been accepted as circumstantial evidence for the presence of tumour suppressor gene (TSG) in human malignancies.

Several case-control studies have explored diet in relation to ovarian cancer and although the results were not always consistent, there was evidence that animal fat and/or meat may increase the risk to the disease (Cramer *et al.*, 1984; La Vecchia *et al.*, 1987; Shu *et al.*, 1989; Mettlin and Piver, 1990) whereas vegetables and/or beta-

carotene may reduce the risk (Byers *et al.*, 1983; La Vecchia *et al.*, 1987; Slattery *et al.*, 1989; Engle *et al.*, 1991). An effect of increased energy intake in early life, as reflected in increased adult height, could account in part, for the increased incidence of ovarian cancer over the last few decades in Japan and Singapore (Tomatis *et al.*, 1990).

Previous studies reported no statistically significant association between perineal talc application and risk or ovarian cancer (Harlow *et al.*, 1992) but recently two case-control studies (Chen *et al.*, 1992; Rosenblatt *et al.*, 1992) found positive association. Hair colouring products contain components that are mutagenic and carcinogenic to animals (IARC, 1987). Several studies have suggested that occupational exposure may be associated with hematopoietic cancers (Zahm *et al.*, 1992). A recent study by Tzonou *et al.*, 1993 showed positive association of hair dyes and ovarian cancer.

Endometrial neoplasm

In the present study, the Chinese were found to have the highest incidence of endometrial neoplasm, followed by the Indigenous Groups and the Malays. The peak incidence was in the age group of 51 - 60 years. This is comparable to the study by Parazzini (1991) which showed that the age-specific incidence is seen in women in their late 50s and early 60s. The ASR for endometrial neoplasm in Sarawak was not calculated due to the small number of cases in the study. In the IARC *Incidence of Cancer*, 1998, the ASR for cancer of the uterus in Malaysia for the year 1985 is 4.8.

Among developed countries, the United States recorded the highest ASR for uterus cancer for the year 1990 i.e. 13.0, and followed by Australia, i.e. 9.6. Developing countries in Asia and Japan recorded ASR values from 2.2 to 6.7.

The rates of endometrial cancer are usually higher in Western and developed countries. Developing countries (and Japan) have incidence rates about four to five times lower whereas India and South Asia have the lowest incidence. Studies showed that the incidence of endometrial cancer has been rising in most countries due to the aging of the population.

The role of unopposed estrogens in endometrial carcinogenesis is well established. Any factor that increases the exposure of the endometrium to unopposed estrogen, such as menopausal replacement treatment, obesity, or irregular menstrual cycles, tends to raise the risk of the disease, while factors that lower exposure to estrogens or increase progesterone levels, such as oral contraceptives or smoking tend to be protective.

The association between weight and endometrial cancer risk has been explained in terms of an increased availability of unopposed peripheral estrogens (particularly in the postmenopause period, when aromatization of androgens to estrogens in adipose tissue is the major source of estrogens (Siiteri, 1978) and progesterone is completely lacking) and a lower concentration of sex hormone binding globulin (SHBG) in obese

women, leading to an increased availability of peripheral estrogens to hormone responsive tissues such as endometrium (Enriori and Reforzo-Membrives, 1984).

Cancer of the vulva and vagina

In the present study, cancer of the vulva and vagina made up about 1 - 2 per cent of gynaecological neoplasms cases in all ethnic groups. Secondary vaginal cancer are more common than primary cancer, which arise by direct extension from the cervix whereas squamous carcinoma of the vulva may be associated with syphilis and infection of HSV and/or HPV (Morley, 1992).

5.2 SEROEPIDEMIOLOGY OF HPV 16, HSV-II, CMV AND EBV ANTIGEN IN CERVICAL CARCINOMA

5.2.1 Seroprevalence of HPV 16, E7

HPV 16 is the most prevalent virus and thus far accounts for probably about 50% of all genital HPV infections. HPV infections are ubiqutious and have been found in all populations studied (zur Hausen, 1989). In the present study, the antibody prevalence to the HPV 16 early protein E7 was measured in cervical carcinoma patients and normal pregnant women. The E7 protein was selected because the E7 gene product of HPV 16 is capable of transforming cells *in vitro* (Phelps *et al.*, 1988) and because of its consistent expression in tumour cell (Seedorf *et al.*, 1987; Smotkin and Wettstein, 1986). Furthermore, the HPV 16 E7 antibody reactivity was specific for the HPV 16 E7 polypeptide as oppose to the HPV 18 E7 polypeptide (Jenison *et al.*, 1990).

In the present study, 23% of the cervical carcinoma sera tested were IgG positive to HPV 16 E7. In 1990, by using ELISA, Mann *et al.*, observed 25% of cases of women with cervical carcinoma were IgG positive to HPV16 E7 as compared to 6% in normal controls. The present results also agrees well with those of Jochmus-Kudielka *et. al.*, (1989) who detected serum IgG antibodies to HPV 16 E7 fusion protein in 20.5% of invasive cervical carcinoma cases and in 1.4% to 3.8% of normal controls by using Western blot. Both methods i.e. ELISA and Western blot have been

shown to detect the same or similar activity (Suchánková *et al.*, 1991). IgG antibodies to E7 was shown to be more common in advanced cancer (Reeves *et al.*, 1990).

Compared to IgG and IgM, the IgA response were more associated with cervical neoplasia (Dillner, 1990; Dillner *et al.*, 1989). The present study observed 27% of the cervical carcinoma cases were IgA positive to E7. Dillner (1989), detected IgA antibodies in 73% of women with carcinoma *in situ* (CIN) or cervical cancer and in 22% of women not known to have CIN whereas Mann *et al.*, (1990), identified the presence of IgA antibodies in 15% of cervical carcinoma patients and in 11% controls. Reeves *et al.*, (1990) also demonstrated that IgA antibodies to E7 were significantly more frequent among women with CIN than controls.

The present study also found that 56.5% of cervical carcinoma cases were IgM positive to E7. However, the IgM antibodies are known to be prone to cross-reactions and some of the reactivities showed in the study may be non-specific.

The high antibody prevalence of HPV 16 E7 protein in cervical carcinoma cases observed in the present study supports the earlier reports that antibodies to epitopes on HPV 16 E7 are markers for HPV 16 associated invasive cancer. Since the E7 protein is the most abundant HPV protein in cervical cancer cells (Smotkin and Wettstin, 1987), prevalence of anti E7 in some of the cervical cancer patients is expected.

In the present study, normal pregnant women were observed to have similar seroreactivity against HPV 16 E7 protein to cervical carcinoma patients. Studies conducted on random normal populations with normal Pap smears had demonstrated a 10 to 20% of HPV infection (Lorintz *et al.*, 1986; deVilliers *et al.*, 1987; Wickenden *et al.*, 1987). Detection of HPV-DNA was reported in 29% of a population of women who were referred to a colposcopy clinic and had normal Pap smears (Burk *et al.*, 1986). In a study conducted among pregnant women, Schneider *et al.*, (1987) detected HPV DNA in 28% of the study population compared with 12.5% for non-pregnant controls. In a study by Garry and Jones (1985), clinically apparent HPV infections of the female genital tract were observed to occur more frequently during pregnancy and regress rapidly after delivery.

The normal pregnant women studied in the present study were in their late second to third trimester and about 28.2% were found to be positive to HPV 16 E7. Rando *et al.*, 1989 detected a very high level of HPV-DNA in exfoliated cervical cells obtained during pregnancy (52.5%) and an increased of detectable HPV-DNA in women in their third trimester (46.0%) compared to in women in their first trimester (20.9%). In a report by Alexander Meisels (1992), cytologic HPV infection was found to be more common in the second half of pregnancy i.e. 7.37% compared to 3.07% in the first half of pregnancy. Compared to ELISA used in our study, cytology had been known to underestimates the prevalence of HPV infection (de Villiers *et al.*, 1987).

The finding of the present study supports previous reports which suggested that immunosuppressed individuals are at an increased risk for both HPV infection and development of HPV-associated benign and malignant diseases (Schneider *et al.*, 1987). A natural altered or depressed immunologic state during pregnancy was proposed by Purtillo *et al.*, 1972 whereby a significant reduction was observed in the maternal lymphocyte response to phytohaemagglutinin (P.H.A.) in most pregnant women. Other studies also reported the frequent occurrence of lower genitalia neoplasia which is associated with HPV infection in immunosuppressed women, for example, female renal transplant recipients (Lewensohn-Fuchs *et al.*, 1993; Schneider *et al.*, 1983), and in acquired immunodefiency syndrome patients (AIDS) (Filipovich *et al.*, 1980; Durack, 1981). In addition to immunosuppressed conditions, hormonal effects during pregnancy may play a role in the enhancement of viral infection of expression especially in the second half of pregnancy since estrogens and progesterones show a steady increase during that period. These hormones would directly influence viral regulatory elements as described for the long terminal repeat region of a retroviral genome (Ponta *et al.*, 1985).

5.2.2 Seroprevalence of HSV-II

For over twenty years, HSV-II was counted as one of the oncogenic candidates for cervical carcinoma. Cancer of the cervix has been regarded as a sexually transmitted disease. In the present study, high prevalence rates of antibodies to HSV-II were

shown in cervical carcinoma patients (95.6%). A similar finding by Dillner *et al.*, (1994) reported a 92% of HSV-II/IgG seropositivity among cervical carcinoma cases in a population study in Northern Sweden. A study in Colombia also showed a 72.7% seropositivity for HSV-II/IgG in cervical carcinoma patients (De Sanjose *et al.*, 1994). These results showed that HSV-II infection is common in women with cervical carcinoma, suggesting that HSV-II may also increase cervical cancer risks.

Higher prevalence rates of antibodies to HSV-II in cervical carcinoma patients than in control were repeatedly observed (Brinton, 1992). It has been suggested that synergism between HPV and HSV may be a cause of cervical cancer. HSV-II might also interact with other cervical cancer risk factors include smoking (Winkelstein, 1990) oral contraceptives use (Beral *et al.*, 1988) and parity (Brinton, *et al.*, 1989).

HSV is also known to contain regions in its genome capable of transforming cells *in vitro*, suggesting a possible oncogenic potential *in vivo*. Papillomavirus transactivator protein E2 was found to be able to activate expression of the promoter/regulatary region at the transforming large sub-unit of HSV-II ribonucleotide reductase (Wymer and Aurelian, 1990). An interaction between HSV-II and HPV 16/18 in the development of cervical neoplasia have been demonstrated by Hildesheim *et al.*, (1991) and Di Paolo *et al.*, (1990). However, de Sanjose *et al.*, (1994) did not find any interaction between HPV and HSV-II.

Primary infections with HSV-II acquired by women during pregnancy account for about half of the morbidity and mortality from HSV-II among neonates. The other half results from reactivation of old infections (Whitley *et al.*, 1988; Whitley *et al.*, 1991). About 70% of the mothers of infants with neonatal HSV infections are asymptomatic at delivery and have no history of genital lesions. Nevertheless, the majority of these women have serologic evidence of HSV-II infection (Whitley *et al.*, 1988).

The prevalence of HSV-II seropositivity among normal pregnant women in the present study was found to be very high (84%) though a little lower than cervical carcinoma patients. In a study conducted by Brown *et al.*, (1994), a 37.8% rate of HSV-II seropositivity was observed in a group of pregnant women. Seropravelence studies had indicated that about 30% of pregnant women possess HSV-II specific antibodies in early pregnancy (Kulhanjian *et al.*, 1992; Koutsky *et al.*, 1990). However, only 20 to 30% of such HSV-II seropositive women give a history of genital lesions. Other surveys also reported a 32% of seropositivity rate in pregnant women (Boucher *et al.*, 1990; Nahmias *et al.*, 1990). The exceedingly high HSV-II seropositivity shown in the present study may be due to the small number of samples tested compared to other surveys.

5.2.3 Seroprevalence of EBV

EBV infection is ubiqutious and is present in up to 100% of the population (zur Hausen, 1991). Early infections, usually within the first year of life, are common in developing countries, whereas infections during adolescence are far more common in industrialized countries, accompanied in part by the typical symptoms of infectious mononucleosis (Henle *et al.*, 1968).

The prevalence of EBV among cervical carcinoma patients and normal pregnant women in the study were found to be similar though the rate of seropositivity to the various EBV-associated antibodies were slightly higher among the normal pregnant women. A majority of cervical carcinoma cases and pregnant women were seropositive for IgG anti-VCA antibody whilst only a small percentage were seropositive for IgA anti-VCA and IgG anti-EA. These results concurs with observations made by Norhanom *et al.*, (1987) in a study comparing EBV serology of a normal population of East Malaysia and NPC patients. When comparing the different class of immunoglobulin to EBV, there appears to be a similar pattern of EBV-seroepidemiology among cervical carcinoma patients, pregnant women and the normal population.

The low IgG anti-VCA antibody titres and extremely low IgA anti-VCA and IgG anti-EA antibody titres observed among cervical carcinoma patients and normal pregnant women were also observed in healthy controls to NPC patients (Henle and

Henle, 1976; Yadav *et al.*, 1987 and Norhanom *et al.*, 1987). The high prevalence of IgG antibodies to the viral capsid antigen in the population studied are merely a signal of EBV infection in healthy controls (Henle and Henle, 1979; Dillner and Kallin, 1987). IgA antibodies to the EBV viral capsid antigen are sensitive markers for EBV-carrying NPC (Henle and Henle. 1976).

The association between EBV and the human uterine cervix is not very well defined. It has been proposed that as in the development of Burkitt's and non-Hodgkin's lymphomas where abnormal population occurs in EBV-infected lymphoid cells, infected cervical epithelial cells may also show a similar exchange. This is supported by the detection of EBV in cells obtained from cervical scrapings and by studies showing an association between cervical cancer and EBV infection (Se Thoe *et al.*, 1993; Schmauz *et al.*, 1989). An association between EBV and squamous cell carcinoma of the cervix was also reported by Landers *et al.*, (1993).

5.2.4 Seroprevalence of CMV

High prevalence of CMV infection has been shown in many populations by serological tests. Due to the high prevalence it is difficult to demonstrate a correlation between CMV infection and cervical carcinoma though CMV has been shown to transform a variety of cells *in vitro* (Razzaque *et al.*, 1991; Jariwalla *et al.*, 1989).

In the present study, both cervical carcinoma patients and pregnant women showed high prevalence of CMV infection. Koffa *et al.*, (1995), found a strong association between CMV and cervical cancer suggesting that past infections with CMV may be a surrogate markers of HPV. However, Thompson *et al.*, (1994) using PCR, failed to detect a direct association or an interaction between CMV and HPV. A high rate of concurrent genital infections with CMV and HPV in cervical cancer patients in Taiwan was reported by Shen (1993). This suggests a synergistic interaction between these two viral infection in the oncogenesis of cervical carcinoma.

Evidence supporting a connection between CMV and transformation of cervical cells has emerged from animal models (Heggie *et al.*, 1986; Nelson *et al.*, 1984; Goldstein *et al.*, 1987). Furthermore, the immediate-early gene products of CMV can transactivate other viral or cellular genes (Boldogh *et al.*, 1991; Colberg-Poley *et al.*, 1991). Since CMV has not been shown to encode any oncogenes, its role in carcinogenesis might centre on its ability to interfere with the regulation of expression of particular host cell proteins perhaps by gene transactivation or repressional mechanisms (MacNab, 1987).

5.2.5 Seroprevalence of HSV-II, CMV and EBV in cervical carcinoma cases according to HPV seropositivity status

In the present study, cervical carcinoma patients were found to have high prevalence of HSV-II and CMV infection regardless of their HPV seropositivity

status. Thus it is not possible to correlate between HSV-II or CMV infection and HPV. A study reported by Jha *et al.*, (1993), demonstrated that the seroprevalence for HSV-II were similar among HPV-seropositive and HPV-seronegative cases. In a study conducted by Koffa *et al.*, (1995), CMV and HSV appear to be significantly associated with cervical cancer. However, among HPV-DNA negative women, only those with CMV or HPV infection were at a significantly increased risk of carcinoma of the cervix. This indicated that past infections with CMV or HSV are surrogate markers of HPV and do not support the view that HPV interacts with CMV and HSV in cervical carcinogenesis (Shen *et al.*, 1993; Hildesheim *et al.*, 1991).

The prevalence for the various EBV-associated antibodies among HPV seropositive cases in the present study were higher compared to HPV-seronegative cases. Previous studies has detected EBV DNA in cervical carcinoma bipsies (Se Thoe *et al.*, 1993). In cervical neoplastic tissues, EBV antigen have been detected using monoclonal immunostaining and immunoblotting (Singh *et al.*, 1989). Landers *et al.*, (1993) found no interaction of EBV in normal cervices, low level of infection in pre-malignant lesions and presence of EBV-DNA in carcinomas of the cervix suggesting that EBV infection occurs late in cervical carcinogenesis and act as a cofactor along with another carcinogenesis agent(s) possibly HPV, in the final progression of malignancy. EBV has been known to have an oncogenic role in the development of other malignancies (Sixbey *et al.*,1986). The presence of viral DNA within the nucleus of malignant cells strongly suggests that EBV has integrated into the host genome making an oncogenic role possible.

CONCLUSION

Descriptive epidemiological study (concerned with describing cancer patterns in different ethnic or geographic communities) is a valuable explorative tool in identifying possible clues of the causative or associative factors of cancers. Although the cancer epidemiology research in Malaysia is greatly hampered by the absence of an organised National Cancer Registry, the publications of hospital-based studies, the first cancer registry in Malaysia i.e. Penang Cancer Registry (1996) and with the establishment of Majlis Kanser Negara (MAKNA) could be the initial steps in developing a National Cancer Registry. In the present study, cervical cancer was shown to be the most common gynaecological neoplasm in all females of different ethnic groups in Sarawak, Malaysia, followed by the endometrium, the ovary and the vulva/vagina. The Chinese was found to be the leading ethnic group in all gynaecologic malignancies. This is closely followed by the Indigenous groups including the Ibans and lastly the Malays. The findings of this study concurs with other previous studies whereby high prevalence of gynaecological neoplasms occurred among the Chinese. Factors that may contribute to the development of cervical cancer are socioeconomic factors such as income and education, multiple sexual partners and infection with HPV and/or EBV. The Muslims practice of prohibition against promiscuity may lower the risks of cervical cancer which was demonstrated among the Malays. The aging of the population runs parallel to the increased in number of other gynaecologic malignancies which may be attributed to reproductive and hormonal effects and also family history of the disease.

The possible association between EBV and HPV as causative factors of cervical carcinoma was observed in the present study. The association of EBV with cervical carcinoma may reflect only a secondary event. Patients with cervical carcinoma may be immunodeficient and thus allow EBV reactivation and replication. The exact role of EBV in cervical carcinoma is yet to be determined, however. EBV may act as a co-factor along with HPV in the progression of cervical malignancy.

Although the present study provided only some basic information, it may be used as a guide to study the pattern of gynaecological neoplasms in the Malaysian population on which further studies and planning may be based.