CHAPTER 1

INTRODUCTION

Cervical cancer represents the fifth most common neoplasm worldwide and comes second after breast cancer as a neoplastic cause of death among women (Parkin et al., 1988). The annual incidence is estimated to be about half a million cases or almost 10% of the six million annual reported cases (WHO report 1987). About 20% of these cases occur in the developing countries where cervical cancer is consistently the leading health problem among women.

In Malaysia due to the lack of a National Cancer Registry, comprehensive information about the distribution and incidences of cervical cancer is still not available. However Norhanom and Yadav, (1995) reported on the prevalence of cancer in the country based on patients seeking radiotherapy and drug treatment for the year 1986. Their observation lists cervical cancer as the second most frequent cancer after nasopharyngeal carcinoma for the country. In females, it ranks first (25.91%), followed by breast cancer (25.58%).

Epidemiological and demographic studies in general have indicated that cervical intraepithelial neoplasia (CIN) and cancer of the uterine cervix are of venereal origin and that a sexually transmitted infective agent is responsible for this disease (Munoz and Bosch, 1989). In the last decade accumulating evidence has implicated some specific human papillomaviruses (HPV) as etiological agents in the development of cervical cancer (zur Hausen, 1986).

HPV are associated with a wide range of clinical, subclinical and latent disease, spanning from benign warts to premalignant and malignant lesions. They are site-specific DNA viruses which induce epithelial or fibroepithelial proliferation

(hyperplasia) of the skin and/or mucosa (Howley, 1990). With the advent of molecular cloning it has become possible to genotype the infective agent and it appears that specific HPV types are associated with anatomically distinct disease.

Of over 70 different types of HPV isolated so far, at least 27 types have neoplastic potentials (de Villiers, 1992). HPV 16, 18, 31, 33, 35, 39, 45, 51, 52 and 56 are commonly associated with high grade CIN lesions and invasive cervical carcinomas. Of these HPV 16 is the most frequently detected type, followed by HPV 18, 31 and 33 (Durst et al., 1983; Hsieh et al., 1988; Boshart et al., 1984; Kulski et al 1987; Beaudenon et al., 1986; Lorincz et al 1986, 1987). The detection rates of HPV 16 and 18 sequences varied widely with some evidence of geographical differences (Fuchs et al., 1988; Yoshikawa et al., 1985; DiLuca et al., 1986; Fukushima et al., 1985). The geographical variation in the prevalence of the different HPV types may account for the difference in their association with the disease occurring in different population inhabiting the different geographical regions of the world (Kulski et al., 1987).

The fact that HPV 16 and 18 DNA may be more than a silent passenger has been demonstrated by its biological activity *in vitro* (Watanabe et al., 1989; Munger et al., 1989) which emphasized the possible role of HPV 16 and 18 in cervical carcinogenesis. Since HPV 16 DNA has also been regularly detected in normal cervices (Griffin et al., 1990; Meanwell et al., 1987; Reeves et al., 1989), it has been suggested that cofactors are necessary for the development of cervical carcinoma . A subset of CIN and cervical carcinoma tissues do not harbour any detectable HPV DNA sequences suggesting that such carcinomas may have evolved independently of any HPV infections (Riao et al., 1990). Further investigations no doubt needed to uncover

the sequence of events during malignant change and the mechanism of involvement of HPV genes and other factors in the genesis of cervical carcinoma.

An aspect of the biology of HPV which is still poorly understood is the humoral immune response to the viral infection. Serological studies could not be performed in the past because papillomaviruses could not be propagated in cell culture systems. In the last few years recombinant DNA technology has shown that this shortcoming may be circumvented (Jenison et al., 1988; Jochmus-Kudielka et al., 1989; Dillner et al., 1989; Norrby et al., 1987). Serology is a powerful tool for the diagnosis of viral diseases and tumours. For example, Epstein-Barr virus (EBV)-associated nasopharyngeal carcinoma can be diagnosed from the detection of IgA antibodies to recombinant EBV proteins (Littler et al., 1991). In addition, the analysis of the humoral immune responses to HPV proteins may be of importance to elucidate the relationship of HPV infections and cervical cancer. An understanding of the immune response to HPV in the long term strategy may be important for the possible intervention of cervical cancer by vaccination (Kochel et al., 1991).

In Malaysia, little is known of the geographic distribution of the oncogenic HPV types 16 and 18 in cervical pathology. The aim of this study is to clarify the frequency of HPV infection in cervical disease ranging from low grade to high grade cervical intraepithelial neoplasia to cervical carcinomas. This was carried out by determining the prevalence and distribution of HPV 16 and 18 DNA in fresh frozen biopsies of cervical carcinoma tissues, non-cervical controls and cervical scrapes from healthy females by the technique of polymerase chain reaction followed by Southern blot hybridization. The prevalence was also studied in formalin-fixed, paraffin-embedded cervical carcinoma and dysplastic tissues by *in situ* hybridization. This study also determines the prevalence and localization of HPV 16 L1 protein expression and HPV

18 E6 protein expression in formalin-fixed, paraffin-embedded cervical intrepithelial neoplasia and cervical carcinoma tissues as well as analyses the serological antibody response to HPV-derived antigens in patients with cervical carcinoma and normal controls.