GUEST EDITORIAL:
PREVENTING CANCERS

Cancer is a leading cause of mortality in developed countries, while in developing countries, including Malaysia, it is increasingly an important problem (Fig. 1). While it is primarily a disease of older persons, it is also seen in children and young adults. Primary prevention of cancer depends upon the identification and modification of aetiologic and risk factors which arise extrinsically in the environment or intrinsically within the body. Secondary prevention of cancer refers to the detection and management of precancerous conditions or the detection of cancer in a stage early enough to effect cure and to prevent the manifold complications of this disease. According to Doll 2 most cancers are amenable to prevention through modification of the environment or behaviour of people in the different age groups. As a result of considerable work in cancer epidemiology, the aetiology of many cancers are being recognised, which if removed or modified may prevent cancer. Exposure to oestrogens especially during menopause can result in malignancy of the corpus uteri, while an excessive exposure to diagnostic or therapeutic x-rays can cause malignancies of the bone and reticulosis. Benzene, ultra-violet light and aromatic amines are known to be responsible for leukaemia, skin cancer and bladder cancer respectively. Removal or minimising these various exposures can help prevent the resulting cancers. 2

AFLATOXINS

Since the first isolation of Aspergillus flavus in 1961, following an outbreak of fatal jaundice in young turkeys traced to a poultry feed containing imported groundnuts contaminated with Aspergillus flavus,3 there has been an increasing interest in the role of aflatoxins in the occurrence of hepatocellular carcinoma in man. It has been shown that people in some areas of the world are frequently exposed to food contaminated with aflatoxins and that a correlation exists between the level of such contamination and the occurrence of hepatocellular carcinoma in areas of the world where the incidence of this cancer is high.4,5 Primary liver cancer, which includes hepatocellular carcinoma, is among the most common cancers in South and South-East Asia, the Pacific basin, and Africa, south of the Sahara.4 It appears that the known areas of high incidence of hepatocellular carcinoma are those where bad storage of dietary staples may provide the critical microclimate for propagation of the fungus and elaboration of the toxin. Though isolations of the toxin have primarily been from groundnuts, it is readily found on rice, maize, wheat and other grains. In Thailand and Africa, up to 65% of groundnuts and 30% of rice sampled were found to be contaminated with the fungus.6 In Malaysia, primary liver cancer appears to be common among the Chinese. In the University Hospital, Kuala Lumpur, the rate of this disease was 33.4 per 100,000 Chinese male inpatients per annum compared to 10.4 per 100,000 Indian male inpatients per annum and 13.5 per 100,000 Malay male inpatients per annum.7 The disease is also common among the Orang Asli, particularly the Senoi (indigenous tribes of the peninsula). Local research on aflatoxins at the Institute for Medical Research8,9 have shown its presence in samples of groundnut oil (46% of samples), shelled groundnuts (58% of samples) and peanut butter (26% of samples). Moir

Fig. 1 Death rates in Peninsular Malaysia for various groups of diseases during the period 1957-1976.
and Verghese indicated that locally-grown groundnuts sold in the shell may contain aflatoxin, while shelled, locally-grown groundnuts are aflatoxin free. Imported preserved plums have been found to contain high levels of aflatoxin, while rice, soya beans and soya sauce have in the past been found to be free of toxin. The probable higher exposure of the Chinese community, compared to the others, to preserved plums, groundnuts and groundnut products, as well as groundnut oil may explain partly, the higher levels of primary liver cancer among them. Measures directed at aflatoxin contaminated foods can help in decreasing the occurrence of this disease. According to Sumitran, an 'aflatoxin committee' under the Malaysian Scientific Association, had in 1966 recommended to the Ministry of Health to prohibit the sale of aflatoxin-contaminated foods, but apparently there has been no response to that recommendation. There probably is a need to reactivate interest in aflatoxins so that aflatoxin-contaminated foods will be identified and appropriate measures taken to prevent the growth of aflatoxins by ensuring that carbohydrate foods are stored under conditions that will not allow the growth of aflatoxins.

VIRUSES

Another known risk factor of interest in hepatocellular carcinoma is the hepatitis B virus. Dr H. Mahler, Director-General of WHO, in an opening address at a WHO meeting on 'Prevention of Liver Cancer' said that for the first time now there are unique opportunities to prevent one form of cancer by immunisation, namely liver cancer, which is one of the ten most prevalent cancers in the world. Epidemiological data from case control and cohort studies, and several laboratory investigations indicate that there is a consistent and specific causal association between hepatitis B virus and hepatocellular carcinoma. A prospective study in Taiwan, involving 22,000 middle-aged Chinese males, showed there was a 223-fold excess risk for hepatocellular carcinoma among the 15% who were detected as hepatitis B surface antigen carriers compared to those having no evidence of being carriers. Mothers carrying hepatitis B virus who are hepatitis B e antigen positive are often highly infectious and apparently transmit the infection to their newborn, a proportion (90%) of whom will become carriers. In Asia, 30-50% of hepatitis B surface antigen carrier-women of childbearing age are hepatitis B e antigen positive, and perinatal infections may account for about half of the carriers in the population, predisposing them possibly to liver cancer. Studies are underway presently to evaluate the immunogenicity and efficacy of hepatitis B virus vaccine given alone or in combination with hepatitis B immunoglobulin. In a study in Japan of 231 infants, a protection in the carrier state of 90-99% was demonstrated after follow up for at least 12 months, while in Taiwan, 95% of infants given both the vaccine and immunoglobulin and 75% of those given only the vaccine at the age of one week received protection. With the existing evidence regarding the vaccine, it would seem that we have the means to prevent primary liver cancer resulting from hepatitis B virus exposure.

A virus of particular interest in Malaysia is the Ebstein-Barr virus, a natural host of the oropharynx. Patients with nasopharyngeal carcinoma, which is common in this country especially among the Chinese, are known to have high serum anti-Ebstein-Barr virus antigen antibody titres. The association between this virus and nasopharyngeal cancer is based on the presence of viral finger prints in tumorous epithelial cells, and a strong immune response of patients to all Ebstein-Barr viral antigens. According to De The, the possibility that chemical carcinogens may play a role in nasopharyngeal carcinoma has also been repeatedly suggested but up to the present there is a lack of epidemiological evidence. The eating of salted fish at an early age appears to be associated with an increased risk of developing this disease and might operate through exposure to nitrosoamines. Successful prevention of nasopharyngeal carcinoma with vaccines will require greater knowledge of the complex interaction of the agent, host and environment to precisely defined risk factors in various populations.

Herpes simplex virus-2 is said to have oncogenic potential and has been associated with human cervical carcinoma. The virus is capable of residing in the genital tract of both males and females, having been isolated from the smegma of males and urinary sediment of females. Both Nahmias et al., and Rawls et al., showed that viral transmission between the sexes occur by sexual contact. Thus females developing cervical carcinoma from exposure to Herpes simplex virus-2 may have had contact with either multiple partners.
or a single male partner who has had contact with several females. While the former possibility has been studied, the latter does not appear to have been adequately evaluated. Graham et al., have shown that women with only one or no sex partner in their history had increased risks of cervical carcinoma, if evidence of antibodies to Herpes simplex virus-2 was present, and that the same was also true for women with two or more sex partners.

Further evidence for an association between Herpes simplex virus-2 and cervical carcinoma is based on serological data which have shown that cases of cervical cancer have higher antibody levels to the virus than controls. In addition, exfoliated cervical carcinoma cells have revealed Herpes simplex virus-2 antigens using immunofluorescent techniques. Catalano and Johnson in their longitudinal study of 15,000 women have shown the development of carcinoma in situ among women with prior Herpes simplex virus-2 infection. Similarly Nahmias et al., showed that after one to six years of follow up, dysplasia developed twice as frequently and carcinoma in situ eight times as frequently among women with prior genital herpes infection as compared to those without prior infection.

According to Nahmias et al., despite the evidence, control of Herpes simplex virus-2 is hampered by the limited knowledge of the interacting immune response that determine the outcome of the primary infection, maintenance of latency and reactivation, as well as the possibility that Herpes simplex virus-2 could be considered as a cofactor in inducing cervical carcinoma. A similar view is held by De The who feels that herpes virus infection probably constitutes an epidemiological marker for the risk of developing the tumour rather than being a causal factor. Hence, while intervention measures may be directed at the virus, the other environment cofactors should not be neglected, the prevention of which will also prevent cervical cancer.

Recently, condyloma acuminatum has received attention as a concomitant of dysplastic cervical lesions. Cytopathologic data indicate that condylomatous lesions produce cells with dysplastic characteristics. The lesions are caused by a human papilloma virus transmitted by sexual contact and viral particles from these lesions have been identified by an electron microscope. A role for this virus in the development of cervical carcinoma has not as yet been demonstrated.

### OTHER RISK FACTORS OF CERVICAL CARCINOMA

In a recent longitudinal study, Furgyik and Astedt reported that cervical carcinoma was at least four times as common among women with gonorrhoea as compared with controls. According to the authors, a carcinogenic factor acquired at the same time as the gonorrhoeal infection cannot be excluded. The findings corroborate the view that cervical carcinoma is a sexually transmitted disease and that it may possibly be easier to search for and detect the aetiological agent in association with gonorrhoea than in patients with already manifest cervical carcinoma.

Yet another cofactor of increasing interest in relation to this cancer is smoking. Winkelstein put forward the hypothesis that since the effect of cigarette smoking is most importantly manifested by a squamous cell oncogenic response in the lung, there exists the possibility that squamous cell tumours of various sites, including cervical carcinoma, will be associated with cigarette smoking. Wigle et al., as well as other investigators have demonstrated increased risk of cervical carcinoma in current women smokers compared to women who never smoked. However Stellman et al., failed to show a significant association between cervical carcinoma and cigarette smoking after adjusting for age and socioeconomic status. This study has subsequently been criticised by Winkelstein on the grounds that the cases and controls were not representative of any defined population and that due to lack of information, adjustments for sexual activity were not possible. Subsequently a case control study, taking into account these criticisms, was carried out by Clarke, Morgan and Newman. They demonstrated a twofold risk of invasive squamous cell carcinoma of the cervix among current smokers relative to women who had never smoked and that this significant effect of smoking was not diminished by simultaneously adjusting for age, education and indices of sexual behaviour. This association was further supported by the observations that ex-smokers were at lower risk than current smokers and that the risk increased with the amount of cigarettes smoked. While it is not possible for these observational studies to prove a causal relationship between smoking and cervical carcinoma, the consistency of the findings between the majority of studies, the persistence of an elevated relative risk after controlling for known
confounding variables, the presence of a dose-response relationship, the reduction of relative risk for ex-smokers and biologically plausible explanation all support a real association between smoking and cervical cancer. 27 Thus interventions directed at smoking may help prevent squamous cell cancers not only of the cervix but that of other sites such as the lung and bladder. However, it is still possible that smoking may be acting as a marker for some factor not yet identified.

DIET

The type of diet we consume may either predispose us to cancer or protect us from it. 28 Presently the hypothesis of colon cancer aetiology link meat, especially beef consumption, and fats to high risk, and fiber and cruciferous vegetables to low risk. 28 Diets containing a trace element called selenium, ascorbic acid and retinoid, as well as prolease inhibitor containing food such as soybeans seem to have a protective function. It appears that a diet low in cholesterol and fats might aid in protecting against colon cancer. 29

Both clinical and epidemiological observations have shown that alcohol consumption is involved in the aetiology of cancer of various sites in the human body, particularly the mouth, pharynx, larynx and oesophagus. In a survey of 7,518 cancer cases, Williams and Horn 30 observed a positive association between alcohol intake and cancers of the oral cavity and larynx. The incidence of oesophageal cancer varies in different parts of the world and in a recent study reported by Tuyns et al., 31 it was found that there was a linear relationship between the logarithm of risk of oesophageal cancer and daily alcohol consumption. Further the combination of alcohol consumption and smoking increased the risk in a multiplicative manner. Alcohol consumption and its possible association with liver cancer is related to cirrhosis, because the cancer very often is accompanied and preceded by cirrhosis or hepatitis and infection. 32,33 Alcohol consumption has also been reported to increase the risk of pancreatic cancer in a study reported by Burch and Ansari. 34 However, this was not so in another study. 35 Probably alcohol acts as a cocarcinogen in the occurrence of pancreatic cancer. In general, alcoholic patients with cancer have poorer chances of survival and greater chances of developing another primary tumour than do other patients with the same cancer, a finding that is corroborated in a study by Schottenfeld 36 of patients with cancer of the upper digestive system, larynx and lung. The carcinogenic property of an alcoholic beverage may reside in other constituents or cogeners of the beverage other than the ethanol molecule itself. It has been suggested that ethanol may enhance the action of carcinogenic agents such as nitrosamines and polycyclic hydrocarbons which may be found in some food and beverages. 37 In Malaysia, alcoholism at present is not a major problem. However with socio-economic changes, urbanisation and changing life-styles of persons, alcoholism may be an emerging problem in the future. The effects of alcohol on health are multiple, and not merely in relation to cancers. Prevention whether primary or secondary directed at alcohol consumption can aid in protecting the alcohol consumer so that alcohol related problems can be avoided.

As mentioned above, many cancers are amenable to prevention through modification of the environment or behaviour of susceptibles. Exposure to oestrogens, x-rays, benzene, ultra violet light, aromatic amines, aflatoxins, hepatitis B virus, Ebstein-Barr virus, Herpes simplex virus-2, cigarette smoking and alcohol consumption are associated with the development of cancers, and measures designed to avoid such exposure will aid in preventing cancers.

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