COMMENTARY

Grand Challenges in Global Health and the Practical Prevention Program? Asian Focus on Cancer Prevention in Females of the Developing World

Malcolm A Moore[1], Kazuo Tajima[2], Pham Hoang Anh[3], Gulsun Aydemir[4], Partha Sarathi Basu[5], Yasmin Bhurgri[6], Kexin Chen[7], Vendhan Gajalakshmi[8], Kaoru Hirose[2], Alireza Mosavi-Jarrahi[9], Le Tran Ngoan[10], You-Lin Qiao[11], Hai Rim Shin[12], Supannee Sriamporn[13], Petcharin Srivatanakul[14], Shinkan Tokudome[15], Keun-Young Yoo[16], Hiroyuki Tsuda[17]

Abstract

In response to the request for 'Breakthrough Questions' for 'Grand Challenges in Global Health' recently published in Nature, the Asian Pacific Organization for Cancer Prevention should focus its attention on what projects are of the highest priority for integration with its Practical Prevention Program (PPP). The most common female cancers in most of the countries of Asia are carcinoma of the breast, followed by the uterine cervix. While the incidences of breast adenocarcinomas are still generally lower than in the Western world they are rapidly increasing, and squamous cell carcinomas of the cervix are a major problem. Clearly there are many areas which would reward research. One factor which appears of major relevance in the mammary gland case is the diet, and particularly the phytoestrogens included in 'tofu', along with physical exercise. The age at which these could be operating needs to be elucidated, with reference to timing of menarche and menopause, and also breast mammographic density, another predictor of likelihood of neoplasia. In the cervix, the predominant influence is well established to be persistent infection with a high risk 'oncogenic' type of human papilloma virus (HPV). Vaccines therefore hold much promise, but a better understanding of the mechanisms underlying spontaneous clearance of both infection and cervical intraepithelial neoplasia (CIN) of different grades is also essential for optimal intervention. The roles of smoking and antioxidant intake in particular deserve emphasis. In Asia, with the considerable variation evident in both breast and cervical cancer incidence rates, as well as in cultural and other environmental factors, we are in a very favourable position to meet two specific challenges: 1) elucidation of how diet in adolescence determines susceptibility to neoplasia of the mammary glands; and 2) determination of what governs persistence of HPV infection. Realisation of these pivotal research aims, with especial emphasis on the context of the PPP, is our shared goal.

Key Words: Major female cancers - research challenges - prevention - lifestyle - diet in adolescence - HPV infection

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Introduction

In the May 1st issue of Nature, a call for ideas for 'Grand Challenges in Global Health' was published (see **www.grandchallengesgh.org**) in the hope of facilitating important advances against disease in the developing world.

[1]APOCP Coordination Center apocp2000@yahoo.com, [2]Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute ktajima@aichi-cc.jp khirose@aichi-cc.jp, [3]National Cancer Institute, Hanoi anh@nci.com.vn, [4]Izmir Cancer Registry, Ege University gulsunaydemir@hotmail.com, [5]Department of Gynecological Oncology, Chittaranjan National Cancer Institute ceds@vsnl.com, [6]Karachi Cancer Registry, Sindh Medical College yburgri@akunet.org, [7]Department of Epidemiology & Biostatistics, Tianjin Cancer Institute & Hospital chenkexin@21cn.com, [8]Epidemiological Research Center, Chennai gajaerc@rediffmail.com, [9]Cancer Institute, Tehran University of Medical Sciences rmosavi@yahoo.com, [10]Department of Occupational Health, Hanoi Medical University letngoan@hmu.edu.vn, [11]Department of Cancer Epidemiology, Beijing Cancer Institute qiaoy@public.bta.net.cn, [12]Department of Cancer Control and Epidemiology, National Cancer Center Research Institute, Seoul hrshin@ncc.re.kr, [13]Department of Epidemiology, Khon Kaen University supannee@kku.ac.th, [14]National Cancer Institute, Bangkok petchar@health.moph.go.th, [15]Department of Health Promotion and Preventive Medicine, Nagoya City University tokudome@med.nagoya-cu.ac.jp, [16]Department of Preventive Medicine, Seoul National University kyyoo@plaza.snu.ac.kr, [17]Division of Experimental Pathology and Chemotherapy, National Cancer Center Research Institute htsuda@gan2.ncc.go.jp

Table 1. Female Burden of Cancers in Major Organs - Incidences/100,000

Registry	China	India	Indonesia	Iran	Pakistan	Philippines#	Thailand	Vietnam	Ranking
Oral	0.8 (9)R	7.8 (3)	?	6.6 (4)	18.7 (2)	6.0 (8)	4.5 (7)	2.7 (8)	7
Oesophagus	6.0 (6)	5.8 (5)	?	24.9 (1)	6.9 (5)	1.6 (9)	1.3 (9)	0.5 (9)	8
Stomach	14.7 (1)	3.5 (7)	?	5.9 (5)	3.2 (8)	6.4 (7)	1.5 (8)	8.5 (3)	6
Colorectal	9.0 (4)	3.8 (6)	6.3 (3)	2.9 (6)	5.0 (6)	15.8 (3)	7.5 (5)	6.4 (5)	3
Liver	8.0 (5)	?	?	1.8 (9)	3.4 (7)	8.0 (6)	15.5 (3)	4.6 (6)	9
Lung	10.2 (3)	3.1 (8)	4.8 (5)	2.5 (7)	2.8 (9)	17.7 (4)	11.1 (4)	7.9 (4)	5
Breast	12.7 (2)	22.6 (2)	14.8 (2)	12.3 (2)	56.6 (1)	47.7 (1)	16.3 (2)	13.8 (1)	**1**
Ovary	5.3 (7)	5.9 (4)	5.2 (4)	2.5 (7)	9.5 (3)	9.4 (5)	4.7 (6)	4.4 (7)	4
Cervix	1.2 (8)	25.3 (1)	21.7 (1)	7.0 (3)	7.3 (4)	21.6 (2)	20.9 (1)	13.1 (2)	**2**

*Data from Selected Cancer Registries (see text for references) # Data from Parkin et al., 1997 R, rank

The aim is to pose the international health research community with a focused set of critical problems, the 'grand challenges', and fund related research with a large donation committed by the Bill & Melinda Gates Foundation.

This is clearly a good opportunity for ourselves to also focus on areas deserving of particular attention within the field of cancer prevention and for this purpose we here look first at the magnitude of burden in different organs in women. As is evident in Table 1, the two most important sites of female cancers across the countries of Asia, in terms of incidence, are the breast and the cervix uteri (Ahn, 2001; Anh, 2001; Bhurgri, 2001; Deerasamee et al., 2001; Esteban et al., 2001; Gajalakshmi et al., 2001; Mosavi-Jarrahi et al., 2001; Ohshima et al., 2001; Sarjadi and Padmi, 2001; Wang et al., 2001). In our list, only in China and Pakistan are these not both within the top three ranking sites. In addition, breast cancer is very much the most important female cancer in Turkey (Fidaner et al., 2001), Saudi Arabia (Al-Hamdan et al., 2001), Jordan (Qasem, 2001), Oman (al-Lawati et al., 2001) and Malaysia (Rosemawati and Sallehudin, 2001). Only in Mongolia are neither breast or cervix cancer within the top three (Munkhtaivan et al., 2001). Furthermore, trends for increase in incidence over time have recently been demonstrated for most of the populations in India (Yeole and Kurkure, 2003) and also in China (Hao et al., 2002). Importantly, breast carcinoma may occur at a relatively young age in Asians, as reported in Pakistan and Iran (Harirchi et al., 2000; Siddiqui et al., 2000). While cervical cancer is on the decrease in many countries of the world it clearly is also still a major problem. Thus if we are to alleviate the cancer problem in women in Asia we have two major targets on which to focus.

Breast Cancer

General

Concentrating first on the overall leader, cancer of the mammary glands, although there is generally a lower incidence in Asia than in Europe and North America, there are exceptional countries like Pakistan and the Philippines with relatively high rates, pointing to major differences in the impact of risk or beneficial factors in the region. The major question is how this can be explained and provide a basis for practical prevention efforts within the Practical Prevention Program (Tajima and Moore, 2001; 2002). The emphasis might best be concentrated on interactions between dietary and other lifestyle-associated factors and the estrogen/progesterone exposure which is firmly established as underlying neoplasia in the mammary glands (Apter, 1996; Brinton 1996; Henderson et al., 1985; Moseson et al., 1993; Nandi et al., 1995). Insulin may also play a role (Bruning et al., 1992; Kazer, 1995; Kaaks, 1996) and the actions of the two hormones may in fact themselves be closely linked (Apter, 1996; Moore et al., 1998) and both bear a relation to obesity (Stoll, 1995).

Genetic Component

While there is obviously a genetic component in determining risk, particularly in high risk families due to mutations in specific genes (Arms and Venter, 2002; Moynahan, 2002), this can not explain variations at the population level. For example, while Japanese in Japan have a relatively low risk, a recent study revealed that Japanese in Hawai'i are at higher rather than lower risk as compared to other ethnic groups (Pike et al., 2002). However, this is not to say that genetic factors and polymorphisms that influence individual steroid levels and breast density, for example, lack a strong impact on breast cancer risk (Boyd et al., 2002; Ziv et al., 2003).

Risk and Beneficial Factors

a) Reproductive Parameters

The basic hypothesis is that the longer the exposure to ovarian hormones during the reproductive years, the higher the risk of breast cancer (see Fig 1). This has been confirmed in Korea (Suh et al., 1996), where epidemiologic studies have shown that early menarche, late menopause, late full-term pregnancy, and never having had a breast-fed child are

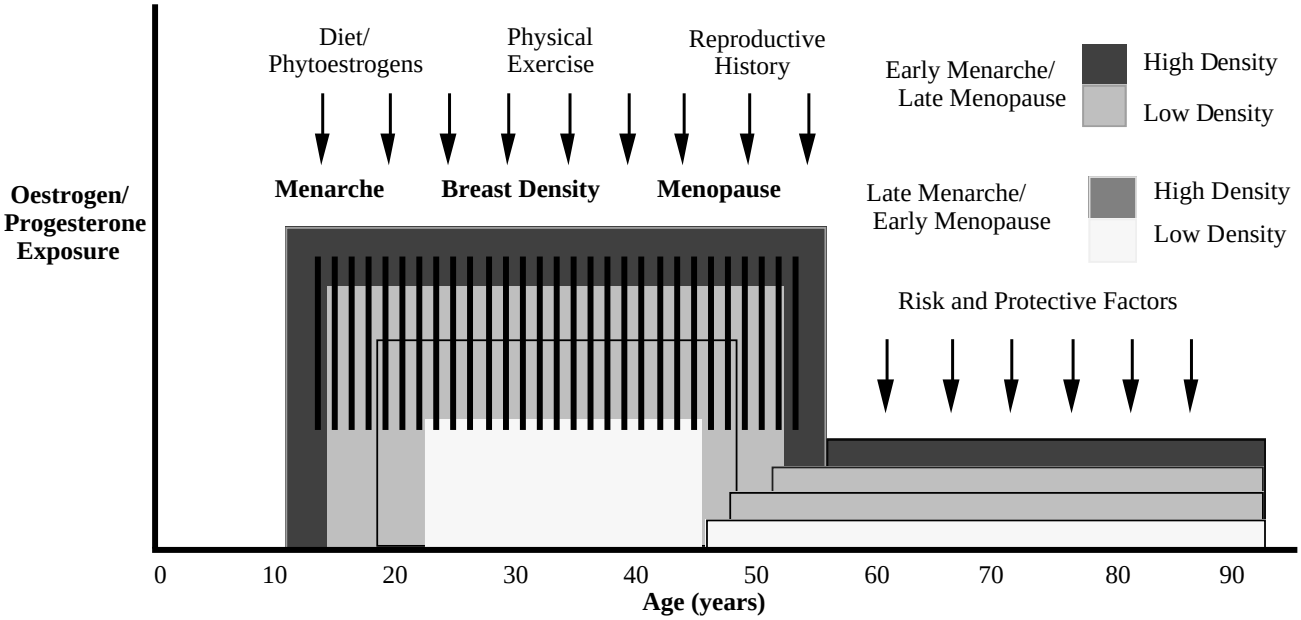

Figure 1. Relationship Between Reproductive Hormone Exposure and Timing of Menarche and Menopause.

primary risk factors in the development of breast cancer (Yoo et al., 2002). Similar findings have been reported from Japan (Hirose et al., 2003b) and India (Gajalakshmi and Shantha, 1991; Gajalakshmi et al., 1998).

Girls experiencing early menarche have earlier and greater increase in follicule stimulating hormone and estrogen, and a drop in sex hormone binding globulin concentrations (Apter, 1996) and delay in menarche of 2 years has been linked to a 10% decrease in risk (Hsieh et al., 1990). After adjustment for BMI and age, women with a late age at menarche (age 17 years or older) showed significantly lower estrogen levels (Wu et al., 2002). While there was no significant association between age at menarche and breast cancer risk in one study in India, a three-fold risk was noted in both pre- and postmenopausal groups when the interval between age at first birth and menarche was more than 12 years (Gajalakshmi and Shantha, 1991). As argued by Russo and co-workers (Russo and Russo, 1994), this is a period when the epithelial tissue in the breast is relatively undifferentiated and susceptible to the actions of carcinogens (see Fig 2).

Parity is clearly protective and this could be operating

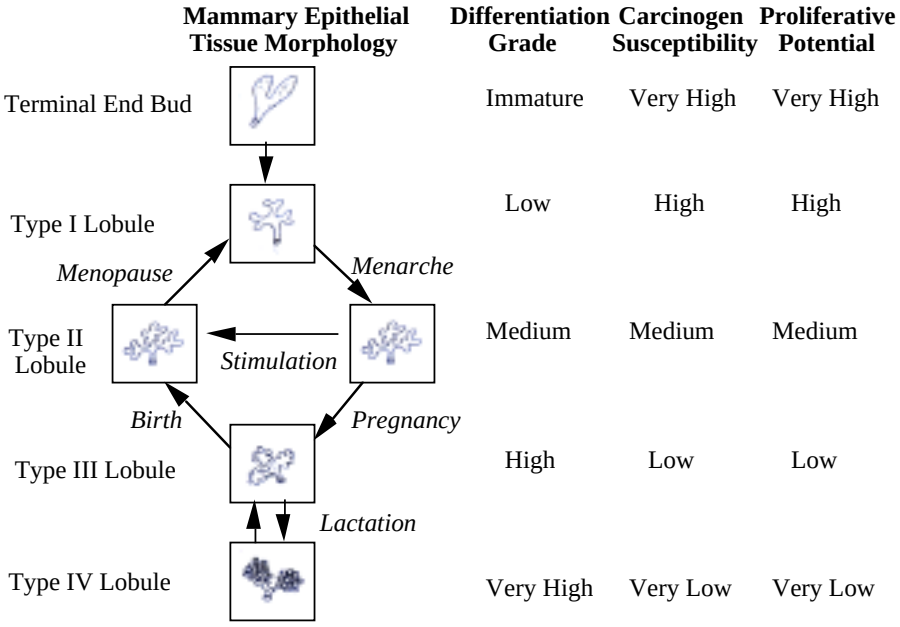

Figure 2. Change in Breast Epithelium Lobule Type with Reproductive Events

via the effects on breast tissue, which becomes more differentiated to allow milk production, as well as on the hormonal milieu. This could be the reason why late age at first childbirth is important and is the rationale for the suggestion by Russo that human chorionic gonadotropin (hCG) be used as a chemopreventive agent to induce differentiation of the lobules. Marital status presumably has an impact on the incidence of breast cancer in Iranian women due to the associated pregnancy (Ebrahimi et al., 2002). Whether lactation itself may exert an independent protective effect against breast cancer remains unclear. Whereas this was concluded for Japanese women (Yoo et al., 1992) it was considered to be simply an association with parity by other workers (Negri et al., 1996).

Exposure to estrogen is dependent on menstrual cycles and risk is decreased when they are greater than 29 days in length in Asian Americans (Wu et al., 1996).Women with irregular (anovulatory) cycles are at decreased risk (den Tonkelaar and de Waard, 1996) and this might partly explain protective effects of physical exercise (Merzenich et al, 1993) and premenopausal obesity (Roland et al., 2002). Long and irregular cycles appear less common with advancing age and more common with menarche after age 14, and with increasing body mass index while smoking is associated with short cycles (Roland et al., 2002). Late menopause may simply increase the number of cycles of exposure and therefore act as a risk factor.

b) Mammographic Density

Estrogens increase and anti-estrogens decrease breast density and this parameter may therefore serve as a biomarker of estrogenic or anti-estrogenic effects of a treatment on breast tissue (Atkinson and Bingham, 2002). In fact, mammographic density is also an independent predictor of risk, for example in African-American and Asian-American as well as white women (Ursin et al., 2003). Higher breast stem mass due to adolescent nutrition, is a risk factor (Chie et al., 1996) and also breast tissue density and volume may be positively associated (Kato et al., 1995). In a Swedish investigation small breast size but a high risk parenchymal pattern was linked to cancer development (Therfjell et al., 1996). In another study, relative to women with breasts consisting entirely of fat, the weight-adjusted odds ratios for women with heterogeneously dense and extremely dense breasts were 2.3 and 4.5 respectively (Lam et al., 2000). While racial differences in breast density may not directly conform to differences in race and age-specific breast cancer incidence rates (El-Bastawissi et al., 2001), low risk American Indian women show a much earlier shift to a lower density parenchymal pattern than Anglo or Hispanic women (Hart et al., 1989).

Many of the factors which impact on estrogen exposure also may affect breast density. Nulliparity or older age at first birth are strongly associated with density among women (El-Bastawissi et al., 2000). Inverse relations with body mass index, high-density lipoprotein cholesterol (HDLC), age at menarche, and soy intake have been described, as well as direct relations with estrogen use and family history (Maskarinec et al., 2001). It should be borne in mind that breast tissue is less radiographically dense in the follicular phase than in the luteal phase, both for screening and comparison purposes (White et al., 1998).

Alcohol and Smoking

In developing countries, where alcohol consumption by females is generally very low or lacking, alcohol would have a negligible effect on the incidence of breast cancer. A major cooperative effort concluded that smoking has little or no independent effect on the risk of developing breast cancer; while the effect of alcohol needs to be interpreted in the context of its beneficial effects, in moderation, on cardiovascular disease and its harmful effects on cirrhosis and cancers of the mouth, larynx, oesophagus and liver (Hamajima et al., 2002). However, current smokers may exhibit significantly higher estrogen levels than nonsmokers (Wu et al., 2002).

c) Dietary Factors

It has been reported that decrease in the trend for breast cancer is associated with intake of bean curd (soy), green-yellow vegetables, and potato or sweet potato, chicken and ham or sausage in premenopausal women, while in postmenopausal women a more frequent intake of boiled, broiled and/or raw fish (sashimi) is beneficial (Hirose et al., 1995; 2003). Regular green tea consumption may be preventive against recurrence of breast cancer in early stage cases (Inoue et al. 2001) and Indian women with cancer of breast or of other sites might have low intake of green-yellow vegetables rich in fiber and carotenoids such as beta-carotene and zeaxanthin and lutein (Ito et al., 1999). Fried foods present as a risk, along with coconut or buffalo milk, while fish and mango are protective (Gajalakshmi, 2000). Fat intake might be an important determinant of breast cancer among populations with a low fat diet, as for example in Indonesia. (Wakai et al., 2000).

Both epidemiological and experimental studies have provided a convincing body of evidence that soy products, including genistein, can protect against breast cancer (see Tsuda et al., 2003, for a recent review). In a study in Chinese in Singapore, soy intake was demonstrated to be significantly associated with decrease in plasma estrogen levels (Wu et al., 2002). Reduction of circulating steroids was also reported by Lu et al (2000) and a dietary supplement of isoflavones moderately decreased serum-free estradiol and estrone levels and increased menstrual cycle length and the mean follicular phase (Kumar et al., 2002). However, another study did not support the hypothesis that isoflavones affect the ovulatory cycles of premenopausal women over a 1-year period. (Maskarinec et al., 2002). It remains unclear what influence soy products may have on age at menarche and menopause. However, in a population-based, case-control study of breast cancer among Chinese, Japanese and Filipino women in Los Angeles County, risk was found to be significantly inversely associated with soy intake during adolescence or adult life,

Table 2. Grand Challenge 1: What Adolescence/Early Adult Factors Determine Susceptibility to Premenopausal and Postmenopausal Breast Cancer Development?

Research Approaches
Questionnaire: Anthropomorphic Factors (Height, Weight, BMI, Fat Distribution)
Lifestyle Factors (Smoking, Diet, Exercise, Sexual Behaviour, Disease and Reproductive History)
Screening: Palpation, Mammography
Assessment of Biomarkers: Nutrients, Serum Markers, Female Hormones, Genetic Polymorphisms
Specific Questions to be Answered
What is the influence of maternal nutrition and birth weight on risk factors for breast cancer?
What is the impact of dietary factors on age at menarche and menopause, as well as hormone levels?
What is the impact of physical characteristics and exercise on age at menarche and menopause, and hormone levels?
What is the relationship between mammographic density and lobule type?
How does genetic background modify the risk impact by lifestyle factors for cancer?

with best protection found for consumption throughout (Wu et al., 2002). Adolescent soyfood intake was also inversely associated with breast cancer risk for women in the highest soyfood intake group in both pre- and post-menopausal women (Shu et al., 2001).

After adjustment for energy intake and other potential confounders, dietary soy protein intake may be inversely related to a high-risk parenchymal pattern (Jakes et al., 2002). Another mechanism by which isoflavones could exert cancer-preventive effects may involve modulation of estrogen metabolism away from production of potentially carcinogenic metabolites to more readily disposable forms (Xu et al., 2000).

d) Physical Exercise

Physical exercise, especially exercise twice a week or more, reduces the risk of breast cancer among Japanese women (Hirose et al., 2003). In a review of the literature for the mammary gland, Friedenreich and Rohan(1995) concluded that epidemiological studies overall pointed to a decreased risk of cancer although they stressed methodological limitations in many cases. Strenuous exercise in adolescence or young adulthood appears to be of major benefit (Mittendorf et al, 1995; Marcus et al, 1994) and can delay onset of the menstrual cycle or cause anovulation (Merzenich et al, 1993).

e) Anthropomorphic Parameters

Height is known to be associated with an increased risk of breast cancer (Ziegler et al., 1997) and an early age of adult height achievement is also a risk factor, independent of age of menarche (Li et al., 1997). In this context it is of interest that those experiencing puberty during the war are at a lower risk of breast cancer (Tretli and Gaard, 1996). In the exteme case, exposure of teenagers to the Dutch famine of 1944-1945 resulted in reduction in adult mammographic density (Van Noord et al., 2002). Height and obesity are in fact independent risk factors for post-menopausal cancer (Hsieh et al., 1990). Whereas a high body mass index might be protective in premenopausal cases, it has generally been found to be promotive for post-menopausal mammary neoplasia (Franceschi et al., 1996; Hirose et al., 1999; Lam et al., 2000). Estrogen levels are increased with a high body mass index (Wu et al., 2002) but obesity may in fact be important for both ER positive and negative tumours (Yoo et al., 2001). Body weight and body mass index (BMI) are inversely related to SHBG level in both premenopausal and postmenopausal women and progesterone might be related to body mass in premenopausal women (Yoo et al., 1998).

f) Pharmaceutical Factors

Tamoxifen has not only proved to be a valuable treatment for estrogen receptor (ER)-positive breast cancer, but is also a pioneering medicine for chemoprevention in high-risk pre- and postmenopausal women. Insights into the pharmacology and toxicology of tamoxifen have led to the recognition of selective ER modulators (SERMs) with estrogen-like actions in maintaining bone density and in lowering circulating cholesterol, but antiestrogenic actions in the breast (Park and Jordan, 2002). Among women receiving tamoxifen, 16 of 36 (44.4%) changed to a parenchymal pattern of lower density (Brisson et al., 2000).

Conclusions - a Grand Challenge?

What are the implications of the above findings then for our Grand Challenge? As listed in Table 2, there are a number of important questions which remain to be answered and research approaches which are available for their elucidation. Since studies of migrants have shown that the adolescent period may be of particular importance regarding breast cancer (Shimizu et al., 1991), as well as obesity (Dietz, 1999), concentration on the years prior to menarche and the period before first pregnancy would appear to be very warranted. In particular the influence of dietary components, like soy products, as well as physical exercise and anthropometric parameters, on timing of menarche and production of steroid hormones may be of essential significance. Given that age at marriage and first pregnancy are generally defined by socioeconomic factors, these can also be a focus of attention. Then our first challenge is:

What Adolescence/Early Adult Factors Determine

Susceptibility to Premenopausal and Postmenopausal Breast Cancer Development?

In this context it should also be borne in mind that birth weight and intrauterine development may have a lasting influence (Yajnik, 2000).

A two pronged approach is envisaged, with one community-based emphasis on lifestyle characteristics and hormonal characteristics of young females in the different countries of Asia, supported then by case-control studies of pre- and postmenopausal breast cancer cases in the same countries and communities.

Attention might also need to be drawn to the type of cancer. Regarding the tumor histogenesis in African-American women, the odds of ductal carcinoma were found to be twice that of lobular carcinoma, compared with Caucasian women (Klonoff-Cohen et al., 1998). Similarly, Asian and Hispanic women also had higher, non-statistically significant odds of ductal versus lobular carcinoma. Whether the outlined research should be combined with promotion of mass screening, taking into account cultural attitudes (Sadler et al., 2001), which has been shown to contribute to the reduction of mortality from breast cancer in Japan (Kuroishi et al., 2000), remains to be determined. However, it has been argued that evidence is insufficient to justify population-based breast cancer screening by mammography for women in Hong Kong and other Asian populations with low breast cancer prevalence (Leung et al., 2002).

Cervical Cancer

General

In Asia, highest levels of cervical cancer are found in India, Indonesia and Thailand, whereas Pakistan and Iran have intermediate incidences and the neoplasm is relatively rare in China. It should be remembered that high parity increases the risk of squamous-cell carcinoma of the cervix among HPV-positive women and general decline in parity might therefore partly explain the reduction in cervical cancer recently seen in many countries (Munoz et al., 2002).

Causal Factor

The main 'cause' of SCC of the uterine cervix is persistent infection with one of the 'oncogenic' human papilloma viruses (HPVs) (zur Hausen, 2002) although cofactors may be necessary for initiation and to allow the virus to generate lesions which progress to cervical cancer. The prevalence of high risk forms of the virus in Asian popultions has been well documented (Ghim et al., 2002; Anh et al., 2003; Shin et al., 2003). HPV-16-immortalized genital cells are known to be responsive to the genotoxic action of known chemical carcinogens (polycyclic hydrocarbons, alkylating agents or cigarette smoke condensate)(DiPaolo et al., 1996), including examples found in cigarette smoke (Nakao et al., 1996). Furthermore, inflammation may be associated with high-grade lesions in women infected with oncogenic HPV (Castle et al., 2001). Chlamydia trachomatis infection is also a possible cofactor in the etiology of squamous cervical cancer, and its effect may be mediated by chronic inflammation (Smith et al., 2002b).

Infection with human papillomavirus precedes the development of low and high grade squamous intraepithelial lesions and the effect of genital HPV infection on CIN development is highly influenced by oncogenic viral type and high viral load (Ho et al., 1998). A sustained high viral load is consequently informative for progression to a high-grade lesion (van Dui et al., 2002). For the latter the risk is greatest in women positive for the same type of HPV on repeated testing (Kjaer et al 2002). Most infections clear spontaneously, however, and a large proportion of the women who were HPV-positive appear to have cleared the infection after one year (Sellors et al., 2003). The rate appears to be slower with high risk forms. Thus the reported median time to clearance of infection with oncogenic strains is 9.8 months, as compared to 4.3 months with non-oncogenic strains (Giuliano et al., 2002a). Surgical treatment of CIN usually results in clearance of HPV infection within 3 months and human papillomavirus DNA testing may be useful as a rapid intermediate end point for monitoring the efficacy of treatments (Elfgen et al., 2002). On average, HPV DNA detection persists longer than related cytologic abnormalities (Schiffman et al., 2002).

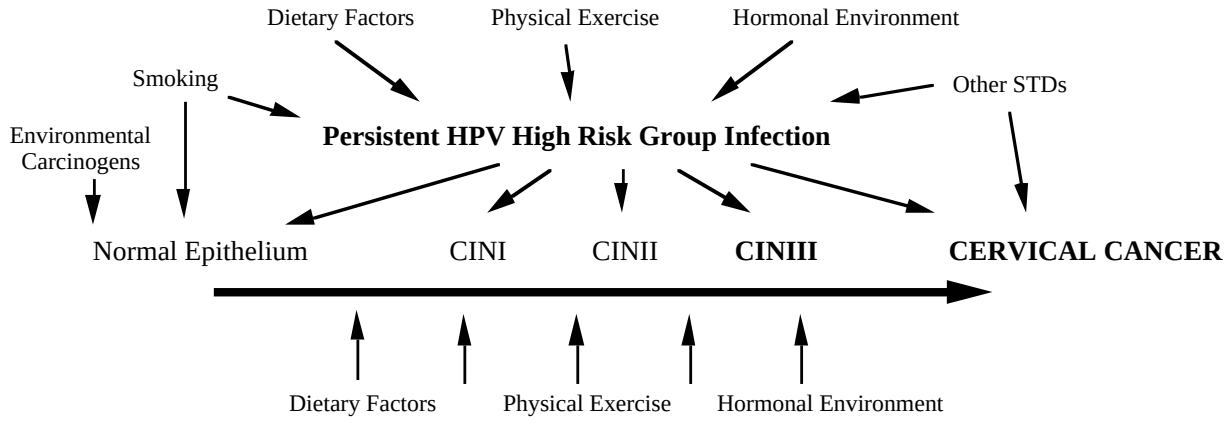

Figure 3. Factors Impacting on Persistent HPV Infection and Cervical Cancer Development

Similarly to the virus itself, human papillomavirus (HPV)-associated cervical intraepithelial neoplasia(CIN) lesions in normal women may spontaneously regress, but a small number obviously do persist and progress to invasive cancer. Neutralizing antibodies against oncogenic human papillomavirus are a possible determinant of the fate of low-grade cervical intraepithelial neoplasia (Kawana et al., 2002) and cellular immunity to HPV-16 E7 is significantly associated with clinical and cytological resolution of HPV-induced CIN (Hopfl et al., 2000). Cell mediated immune responses to E7 peptide correlate significantly with regression of disease and with resolution of viral infection within 12 months (Kadish et al., 2002).

Risk and Beneficial Factors

Sexual Behaviour

a) Direct Influence on Cervical Cancer Development. It has been suggested that HSV-2 infection may act in conjunction with HPV infection to increase the risk of invasive cervical carcinoma on the basis of an analysis of seven case-control studies (Smith et al, 2002), although in other studies, it was concluded that the virus did not play a role in cervical carcinogenesis. (Lehtinen et al., 2002; Tran-Than et al., 2003). As noted above, other sexually transmitted diseases could also play roles as co-factors.

b) Influence on HPV Infection. Incident infection with carcinogenic HPV has been shown to be highest in sexually active women aged 15-19 years, and risk factors are consistent with a sexually transmitted infection. Lifetime number of sexual partners is associated with oncogenic HPV infection. In contrast, nononcogenic HPV infection appeared to be associated with recent sexual activity, suggesting that nononcogenic infections may be more transient (Giuliano et al., 2002b).

Hormones

a) Direct Influence on Cervical Cancer Development. Long-term use of oral contraceptives could be a cofactor that increases risk of cervical carcinoma by up to four-fold in women who are positive for cervical HPV DNA (Moreno et al., 2002). However, it has been concluded that there is no evidence for a strong positive or negative association between HPV positivity and ever use or long duration use of oral contraceptives (Green et al., 2003)

b) Influence on HPV Infection. Included in factors that may predispose to persistent, oncogenic HPV-16 or -18 infection are estrogens, or progestins in the presence of estrogens.(Thomas et al., 2001)

Smoking

a) Direct Influence on Cervical Cancer Development. Cigarette smoking is a factor, which, independently of HPV infection, influences the treatment outcome of CIN (Acladius et al., 2002). The finding that burning wood in the kitchen as also a risk factor is interesting in this context (Velema et al., 2002).

b) Influence on HPV Infection. Smoking may promote early cervical carcinogenic events by increasing duration of oncogenic HPV infections and decreasing the probability of their clearance (Giuliano et al., 2002c).

Diet

a) Direct Influence on Cervical Cancer Development. It has been suggested that high plasma levels of antioxidants may reduce the risk of cervical SILs independent of HPV infection (Goodman et al., 1998). Lycopene and perhaps vitamin A may play a protective role in the early stages of cervical carcinogenesis. (Kanetsky et al., 1998) and vitamins C and E (alpha-tocopherol) appear to independently exert protective effects against development of CIN (Ho et al., 1998). The latter vitamin was found to be significantly inversely associated with grade of cervical dysplasia (Giuliano et al., 1997). In another study, dietary intake of foods rich in total vitamin A, and particularly those with high-retinol content, reduced the risk of in-situ cervical cancer, and at the highest level of intake may inhibit progression to invasion (Shannon et al., 2002).

b) Influence on HPV Infection. In one study, concentrations of serum beta-carotene, beta-cryptoxanthin, lutein, and alpha- and gamma-tocopherol were significantly lower among women two times HPV positive compared with either two times HPV negative or one time HPV positive (Giuliano et al., 1997). Circulating vitamin B12 levels also demonstrated an inversely associated with HPV persistence after adjusting for age, age at first intercourse, marital status, cigarette smoking status, race, and body mass index. No significant associations were observed between HPV persistence and dietary intake of folate, vitamin B12, vitamin B6, or methionine from food alone or from food and supplements combined or from circulating folate in another case, however(Sedjo et al., 2002).

Pharmaceutical Intervention

a) Direct Influence on Cervical Cancer Development. The cervix has many advantages as a target for chemoprevention of squamous cell carcinogenesis (Mitchell et al., 1995). Premalignant lesions are readily identifiable and can be readily followed. Direct application of preventive agents is feasible, with the possibility of repeated biopsy. As a marker, Ki-67 immuno-quantitation in CIN 1 or CIN 2 has strong independent prognostic value for progression (Kruse et al., 2003).

Regarding trials which have already been performed, intravaginal dehydroepiandrosterone was found to be safe and well tolerated and to possibly promote regression of low-grade cervical lesions (Suh-Bergmann et al., 2003). A statistically significant regression of CIN in patients treated with indole-3-carbinol orally compared with placebo has also been reported (Bell et al., 2000), although in another study, the antioxidant beta-carotene did not enhance the regression of high-grade CIN, especially in HPV-positive subjects (Keefe et al., 2001).

b) Influence on HPV Infection. Antiviral agents like Cidofovir have potential for treatment of severe HPV-

Table 3. Grand Challenge 2 - What Lifestyle Factors in Early Sexually Active Life Determine Persistence of Oncogenic HPV Infection?

Research Approaches
Questionnaire: Lifestyle Factors (Smoking, Diet, Exercise, Cooking/Work Environment, Sexual Behaviour, Disease and Reproductive History
Screening: HPV Testing, Pap Smear (Self/Non-self Sampling), Direct Visual Acetic Acid
Biomarkers: Serum Nutrients, HPV Antibodies, Hormones
Specific Questions to be Answered
What variation is there in antioxidant intake and what is its impact on persistence of HPV infection?
What variation is there in physical exercise and what is its impact on persistence of HPV infection?
What are the effects of trauma and STDs on HPV persistence?
What is the relationship between HPV infection and habitual smoking?
How does genetic background modify the risk impact by lifestyle factors for cervical cancer?
What socioeconomic factors impact on sexual behaviour?
Is there inter-country or inter-region variation in high risk HPV and CIN prevalence?
What is the most economic and socially acceptable approach for cervical cancer screening?
How effective is vaccination and how can programs be best developed?

induced proliferative lesions in the cervix, as well as in other sites of the body (Snoeke et al., 2001). Intramuscular injections of interferon beta are effective for treating recurrent HPV, particularly when associated with CIN (Gonzales-Sanchez et al., 2001). Topical immunotherapy is also conceivable (Hengge et al., 2001). It has been argued that chemopreventive agents to decrease HPV viral protein expression warrant particular attention (Follen et al., 2002). Finally, in the future, the possibility of applying specific vaccines will become increasingly feasible and indeed, the first steps have already been taken (Koutsky et al., 2002). If HPV vaccines are successful, the balance of cervical cancer prevention may shifts from traditional screening to primary prevention coupled with HPV testing (Crum et al., 2003).

Conclusions - a Grand Challenge?

The risk factor of over-riding importance for cervical cancer development is persistent infection with oncogenic viruses and initial exposure generally occurs relatively early in sexually active life. Socioeconomic and other cultural determinants are here again of vital importance but it is very likely that the lifestyle of females in their late second and third decades is a major determinant of both whether infections will become established, and if so whether they will persist to become a chronic problem. Therefore our second challenge is:

What Lifestyle Factors in Early Sexually Active Life Determine Persistence of Oncogenic HPV Infection?

As listed in Table 3 there are a number of specific questions that need to be asked and appropriate methodology for our collaborative group to generate evidence-based answers. The proposed research could be integrated with further research into the most appropriate screening approaches for developing countries.

It has also been argued that for this purpose the most effective means for early detection may be direct visual inspection with acetic acid (Wesley et al,. 1997; Sankaranarayanan et al 1998; Chirenje et al., 1999; Singh et al., 2001). A second approach is to concentrate on the viral risk factor and test for HPV strains, especially in high risk populations. However, the results of one recent comparison of PAP, HPV and direct visual methods (Costa et al., 2000) prompted the authors to conclude that no single test can be adopted to replace the PAP smear in routine clinical studies. Choice of test is complicated by cultural variables and in some cases self-sampling may be of assistance in improving compliance (Dzuba et al., 2002). One device for this purpose has already been tested and shown to give reliable results (Pengsaa et al., 1997). Gravitt et al (2001) also demonstrated that a self-collected Dacron swab sample of cervicovaginal cells is a technically feasible alternative to clinician-administered cervical cell collection for studies of the natural history studies of HPV and cervical cancer. Consideration how best these might be applied, within the context of the developing world, is also a question which could be optimally approached within our comprehensive collaborative group setting.

Overall Conclusions

Responding to the two Grand Challenges that we have here described will be dependent on our ability to obtain the necessary financial support as well as establishing the infrastructure. The latter has already been achieved by the members of the APOCP, acting together to draft this commentary, and our professions as academics within Universities and Research Institutes across the Asian region. In the same spirit of cooperation, the members of the APOCP now need to collaborate in the search for grants to allow research plans to be put into practice. That this form of cooperation should be promoted was one of the decisions made at the First General Assembly Conference in 2002 (Moore and Tajima, 2002). Such a comprehensive project would naturally require effective management and

coordination but the benefits would reward the necessary investment - we are facing a gigantic problem with breast and cervical cancer and now is the time to act. The APOCP was set up to perform exactly this type of collaborative endeavour.

Regarding the practicalities of conducting the envisaged research, university students are one natural set of subjects that are of a susceptible age group and accessible. While their education status may mean that they are aware of the problems and more willing to participate in such a research project, they cannot be regarded as typical of the population at large. In addition, it may be necessary to include younger women in order to fulfil eligibility requirements for recruitment (Gudmundsdottir et al., 2003). The importance of education has been stressed, for example to persuade young women to take part in HPV clinical trials (Hoover et al., 2000), and also for mothers of pre-menarche children and/or teenagers who are not sexually active (Lazcano-Ponce et al., 2001). Therefore the idea of the Practical Prevention Project (Tajima and Moore, 2001; 2002), reaching into the community to provide information as well as facilitate access to primary preventive measures is of prime importance. Its further development is an essential prerequisite to the success in meeting our Grand Challenges. Particular emphasis could be placed on use of nurses and midwives for both primary prevention and screening (Turkistanlı et al., 2003).

Clearly, there are many other areas in which cross-country collaboration would greatly benefit cancer prevention in the Asian Pacific, as for example in assessing the relative influence of different genetic polymorphisms in Caucasian as compared with Mongoloid stocks (Hamajima et al., 2002). Formation of APOCP research consortia to promote activity in such specific areas should be one of our major goals.

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