

## Postmenopausal Gynecological Cancers

# The Singapore perspective and its general applicability

- Woon-Puay Koh, MBBS, PhD
- Hin-Peng Lee, MBBS, FFPHM

### International variation

Although breast cancer is the most common malignancy among women worldwide, there is as much as a 10-fold difference in incidence among countries or geographical regions. The overall age-standardized incidence rate of breast cancer in the United States in 2002 was estimated at 101.1 cases per 100,000 woman-years; similar rates were observed in other Western populations such as Canada (84.3), Australia (83.2), New Zealand (91.9), Western European countries (70-90), and in some parts of South America such as Uruguay (83.1) and Argentina (73.9). Conversely, the rates were lowest in countries in Asia and Africa (ranging from approximate-

ly 10 to 30 cases per 100,000 woman-years) (FIGURE 1).<sup>1</sup>

Factors such as differences in the prevalence of screening, access to health care systems, and completeness of cancer registration do not adequately account for this huge disparity. Interestingly, cancers of the uterus and ovary—which are the other 2 most common cancers in women—are strikingly similar in geographical distribution; they are highest in developed countries in North America and Europe, and lowest in Asian and African countries.<sup>1</sup>

The inverse pattern is seen with cervical cancer rates. For this gynecological cancer, 80% of all cases occur in developing countries: rates are highest in South and Southeast Asia, South America, and Africa, and generally low in North American and European populations (FIGURE 2).<sup>1</sup> Cervical carcinogenesis has been linked to human papillomavirus (HPV) infection. Because HPV is a sexually transmitted infection (STI), risk factors for cervical cancer include: having

multiple sexual partners or having a partner with multiple partners; early age at initiation of sexual activity; and presence of other STIs. Cervical cancer has also been associated with low socioeconomic status, smoking, and immunosuppression.

As with all other cancers or diseases with large geographical variation, such disparities in disease incidence can be explained by differences in genetics or by the influences of lifestyle or environmental factors. The observation that migrant populations acquire the rates of host countries provides evidence that changes in lifestyle factors are likely to account for the geographical variation in cancer risk. Indeed, studies of migrant populations have shown that when women migrate from a low-incidence region to a high-incidence region, they acquire the breast cancer rates of the host country within 2 to 3 generations. A comparison of the 1997 age-standardized incidence rates of breast cancer between

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## FROM THE EDITOR



As I write this editorial, the Women's Health Initiative is reporting that women aged 50 to 59 years who use hormone therapy do not have an increased incidence of coronary heart disease.<sup>1</sup> All-cause mortality was reduced by 30% in women in this age-group who used hormones. A dramatic change has occurred since 2002, when the same group indicated that postmenopausal women using estrogen and progestin therapy were at an increased risk for coronary heart disease.<sup>2</sup> It is a sad state of affairs that it has taken 5 years and many untreated women to see the final data analysis vindicate the use of estrogen-only therapy and estrogen and progestin therapy in recently menopausal women.

This issue of *Menopausal Medicine* addresses menopause—and aging in general—in the large and diverse population of Asia and, particularly, Southeast Asia. The ability to live without functional impairment is important for all of us.<sup>3,4</sup> Indeed, the World Health Organization has focused on aging in developed and developing countries, and globally, it is accepted that counseling and interventions for disease prevention will become increasingly important as aging populations grow in the future.

In North America, the percentage of women of Asian origin is large and growing. Accordingly, our practices are becoming more diverse and will continue to do so. Menopause may be common to all women but, based on their experiences in the ethnically diverse community of Singapore, the authors of these 3 articles describe how women experience this milestone differently. Their reports emphasize the need for health care providers to be cognizant of the symptoms, concerns, and therapeutic needs of ethnically diverse populations.

Drs Woon-Puay Koh and Hin-Peng Lee address the marked disparity in breast cancer incidence between Asian and Western populations. US physicians tend to focus on the role of hormones in the initiation and progression of breast cancer; these authors highlight how changes in diet and exercise in Singapore contribute significantly to the rising incidence of breast cancer in that city state. They present fascinating data about the changes in the incidence of breast cancer among migrant populations, eg, breast cancer risk changes when a Japanese woman leaves Japan to live in North America. With assimilation, she faces the same risk of breast cancer as a woman who is native to North America. This thesis emphasizes the role of diet and, possibly, other environmental factors in changing the incidence of breast cancer, using the Singapore experience as a model.

Dr Foo-Hoe Loh evaluates the effect of culture on menopause and, conversely, the effect of menopause on the culture.<sup>1</sup> Singapore represents an ethnic microcosm of South and Southeast Asia. Dr Loh's study of menopause in Singaporean women demonstrates the difficulty of separating cultural values from physiological phenomena. Women in Singapore perceive and respond to menopausal symptoms and physical changes such as vaginal atrophy and dyspareunia differently than do Western women. Perhaps of greater impact than even cultural response to menopause is socioeconomic class. Dr Loh hypothesizes that an affluent woman may have more time to consider symptoms and, consequently, seek therapy than an impecunious woman whose priority is making ends meet.

Dr L K H Koh compares the rates of hip and vertebral fractures in Asian and Caucasian women. The marked difference observed in the incidence of fracture between different ethnic populations remains to be explained. Bone mineral density (BMD) values for osteoporosis appear to be similar in terms of the guidelines for Asian and Caucasian women, though they have been modified for Japanese women. All of the current therapies such as estrogen, raloxifene, and the bisphosphonates appear to be as efficacious in maintaining or increasing BMD for Asian women as they are for Caucasian women. There appears to be equal efficacy for BMD maintenance in Asian women with the use of lower doses of bisphosphonates.

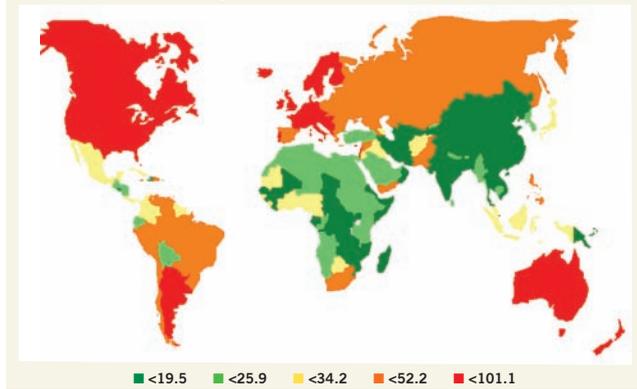
The need for treatment is highly individualized, and it is dependent upon the health care provider being attuned to cultural attitudes and individual needs.

David F. Archer, MD

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FIGURE 1

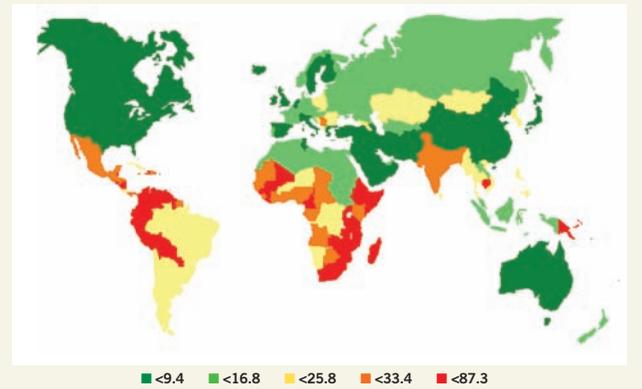
### Breast Cancer: Age-Standardization Incidence Rate per 100,000 Woman-Years (2002)



Provided by International Agency for Research on Cancer through *CANCER Mondial* <http://www-dep.iarc.fr/>

FIGURE 2

### Cervical and Uterine Cancer: Age-Standardized Incidence rate per 100,000 Woman-Years (2002)



Provided by International Agency for Research on Cancer through *CANCER Mondial* <http://www-dep.iarc.fr/>

the migrant Japanese in Los Angeles and native Japanese in the Osaka province of Japan illustrates this. Although the native Japanese women had a low incidence of breast cancer (32.1 cases per 100,000 woman-years), the migrant Japanese had an incidence rate comparable to rates across the United States (85.8 cases per 100,000 woman-years).<sup>2</sup>

Extensive epidemiological evidence has linked breast cancer with reproductive factors that increase estrogen levels, such as delayed first birth, nulliparity, decline in breastfeeding, and the use of hormone replacement, as well as other lifestyle and dietary factors that may mediate through a hormonal pathway. **These risk factors** are more commonly observed in affluent, Westernized societies. Interestingly, many historically low-incidence Asian countries are now experiencing a rapid increase in these cancer incidence rates as they undergo profound social changes in child-bearing, diet, and other lifestyle practices because of industrialization and Westernization.

### The Singapore perspective

Singapore is one of the Asian countries whose cancer rates are on the rise. This small city-nation of about 270 square miles is situated 85 miles north of the equator. The resident population was 3,553,500 in 2005, comprising Chinese

(76%), Malays (13%), Indians (9%), and a minority of people of other races (2%). Between 1968 and 1997, Singapore rapidly transitioned from a developing to a developed nation; the gross domestic product increased by 325% between 1960 and 1980. Often described as sitting at the crossroads between East and West, Singapore's rapid economic advancement has caused major changes in lifestyle that are similar to those experienced by migrant populations moving from developing to developed nations.

### Social and cultural shifts

In Singapore, profound social changes in childbearing (delayed first birth, fewer children) and dietary practices (more meats, fewer grains) have taken place in the past 3 decades. Epidemiological data from the Singapore Chinese Health Study bear this out. Lifestyle factors for chronic diseases such as cancer have been studied in this cohort (established between 1993 and 1998) of 63,000 middle-aged and older Chinese men and women. We have noticed monotonically decreasing mean numbers of children (5.5, 4.3, and 2.9) among women born between the years 1910 to 1929, 1930 to 1939, and 1940 to 1949, respectively. Correspondingly, the mean age at first birth in these 3 successive birth cohorts increased from 23.0 to 24.4 and 25.4 years, respectively. These

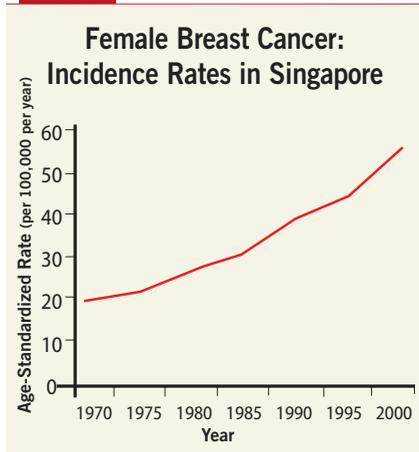
birth cohorts also display monotonically decreasing intake of total grains and increasing intake of total dietary fats.

### Cancer rates in Singaporean women

Among all cancers in women in Singapore, breast cancer has the highest incidence, accounting for 55% of all gynecological cancers from 1998 to 2002. As the most dominant ethnic subpopulation, Singapore Chinese women in particular are currently experiencing one of the highest rates of increase in breast cancer in the world. Over a 30-year period from 1968 to 1997, rates of breast cancer increased 2.7-fold (from 20.0 to 54.9 per 100,000 per year) among Singapore Chinese women<sup>3</sup> (FIGURE 3). In addition, although breast cancer had been more common in women younger than 50 years, a strong birth cohort effect has led to an increase in postmenopausal breast cancer rates and a change in the age-incidence curve to resemble that seen in the West.

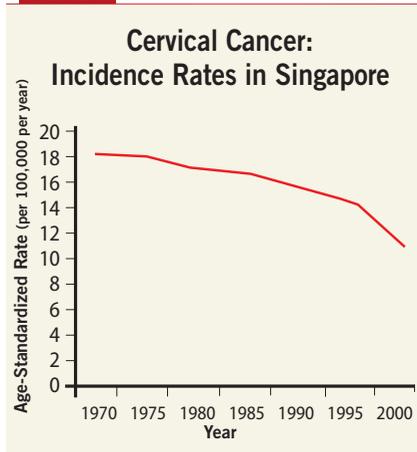
Chia et al compared the marked difference in cross-sectional age-specific rates between Singapore and Sweden from 1968 to 1997; they concluded that the more rapid changes in reproduction and lifestyle patterns among Singaporean women compared with Swedish women accounted for a larger cohort effect seen in Singaporean women. Chia predicted that the incidence of breast cancer in postmenopausal women

FIGURE 3



Age-standardized incidence, 1969-2002.

FIGURE 4



Age-standardized incidence, 1969-2002.

in Singapore will continue to rise in the coming decades to match the rates seen in Western populations.<sup>4</sup>

Currently, in Singapore postmenopausal women account for 53.8%, 64.8%, and 51.8% of cancers of the breast, uterus, and ovary, respectively. Ovarian and uterine cancers have been increasing steadily in incidence over the last 3 decades and now rank fourth and seventh, respectively, among all cancers in Singaporean women. In contrast, incidence rates for cervical cancer have consistently declined over the last 3 decades (FIGURE 4) and this can be partially attributed to the ready availability of Papanicolaou (Pap) testing.<sup>3</sup>

## Control strategies

The approaches for cancer control are primary prevention through the reduction of etiological factors that promote carcinogenesis; secondary prevention by the early detection of cancer through screening; and tertiary prevention in improved treatment to reduce morbidity and mortality associated with cancer.

## Population screening

Effective screening methods are available for breast and cervical cancer. Mammography can detect early breast cancer and has been shown to be effective for breast cancer screening, with a significant 38% reduction in mortality rates for women

aged 50 years and older.<sup>5</sup> While controversies exist regarding the efficacy of mammography among premenopausal women, detailed re-analysis of the Swedish trials in 2002 convincingly showed that screening conferred a breast cancer survival advantage among women in general.<sup>6</sup> Triennial Pap testing is recommended for cervical cancer screening,<sup>7</sup> and well-established screening programs in Nordic countries have been credited with reducing cervical cancer mortality rates by up to 80%.<sup>8</sup>

In Singapore, breast and cervical cancer screening programs started in the 1960s. Most recently, Breast Screen Singapore and Cervical Screen Singapore are government-funded, centrally organized, nationwide programs introduced in January 2002 and August 2004, respectively, to provide subsidized screening mammograms and Pap testing in public hospitals and community-based clinics.

## Overcoming barriers to screening

In order to understand the factors that predict, motivate, and serve as barriers to cancer screening, we recently conducted a population-based cross-sectional survey among 467 women aged 40 to 80 years from 900 randomly selected household units in a residential area in Singapore in 2005. The prevalence of having ever had a mammogram was 46.7% (95% confidence interval [CI], 42.2%-51.2%)

and that of having ever had a Pap test was 64.6% (95% CI, 60.4%-68.6%).

The primary reasons women cited for having been screened for cancer included: strong health-seeking behavior, screening that was part of a routine health check-up, and having received advice from medical professionals. The most significant barriers to screening included self-perceived low-susceptibility to cancer, lack of time, and not wanting to worry unnecessarily. Motivators that would prompt women who had not been screened to go for screening included having received such advice from health care professionals and receiving a subsidy for the tests.

Our study suggests that the medical community should educate women about the importance of screening, increase their perception of self-susceptibility to cancer risk, and enhance the accessibility and availability of screening facilities to promote mammography and Pap testing in Singapore. The findings in this study are applicable to both developed and developing countries.

## Lifestyle and dietary factors

Although it is well established that reproductive and hormonal factors such as parity, age of menarche and menopause, and use of oral contraceptives and hormone replacement affect the risk of breast and gynecological cancers, there is now rapidly growing epidemiological evidence that common lifestyle factors such as obesity and physical inactivity also increase the risk of these cancers. In addition, cigarette smoking, alcohol consumption, and diet also contribute to such risks in women.<sup>9</sup> Although the independent effects of these risk factors for each cancer site must be established more conclusively, there is definitely potential benefit in promoting a healthy diet and physical activity among postmenopausal women to decrease their cancer risk.

In 1997, the American Institute for Cancer Research (AICR) published 14

dietary recommendations and emphasized smoking cessation, in a concerted effort to reduce worldwide cancer incidence. These 14 recommendations included: eating a predominantly plant-based diet rich in a variety of vegetables, fruits, legumes, and minimally processed starchy staple foods; cutting down on consumption of meat, fats, oils, salt, and alcohol; and maintaining a healthy body weight through physical activity.

The benefit of this type of diet in cancer reduction among women was demonstrated through a follow-up study involving 29,564 middle-aged and elderly women in the Iowa Women's Health Study in the United States. At 13 years' follow-up, there was a 31% reduction (95% CI, 19%-37%) in all cancer incidence among women who never smoked and who followed 6 to 9 of the recommendations.<sup>10</sup> Such a significant reduction in the risk attributed to a typical population through dietary and lifestyle modifications has also been shown in other population studies such as the Breast Cancer Detection Demonstration Project cohort in the United States and a Swedish cohort that adhered to a recommended diet of a high variety of fruits, vegetables, whole grain breads, cereals, lean meats, fish, and low-fat dairy products.<sup>11,12</sup>

### Cancer benefits of specific nutrients

Finally, there is increasing scientific interest and evidence—both experimental and epidemiological—in the protective effects of several foods and beverages against breast cancer.

Multiple experimental studies have shown that green and black tea extracts and tea polyphenols such as epigallocatechin gallate (EGCG) can suppress growth of human breast cancer cell lines and reduce carcinogen-induced mammary tumor burden in rats.<sup>13</sup> The mechanism by which green tea extracts and EGCG reduce the level of vascular endothelial growth factor (VEGF) may

be through a pro-angiogenic factor secreted by human breast cancer cells, in a dose-dependent manner.<sup>14</sup>

Clinical studies indicated that consumption of green tea was inversely associated with breast cancer recurrence among Japanese women, especially among those with early stage of this malignancy.<sup>15</sup> Recently, an inverse association was shown between green tea consumption and breast cancer risk among Asian women in Los Angeles, particularly among those consuming few dietary soy isoflavones (a potent antioxidant). These results support the importance of antioxidation by tea constituents in the chemoprevention of cancer.<sup>16</sup>

The hypothesis that dietary fats influence breast cancer risk has been the source of much debate. Experimental studies suggest that n-6 polyunsaturated fatty acids (PUFAs) are metabolized to produce several inflammatory prostaglandins and eicosanoids. These biologically complex compounds may, in turn, promote mammary tumorigenesis by enhancing cell proliferation and growth, promoting angiogenesis, and altering hormonal metabolism.<sup>17</sup>

Within a cohort of 35,000 Chinese women in the Singapore Chinese Health Study, we observed that women in the highest quartile of intake of n-3 fatty acids from fish experienced a 25% lower risk of breast cancer, which was statistically significant. Furthermore, among those consuming low levels of n-3 fats, high intake of n-6 fatty acid was associated with increased breast cancer risk.<sup>18</sup> These observations are consistent with experimental evidence indicating that the protective effect of n-3 PUFAs may be based on its competitive inhibition of n-6 fatty acid metabolism.<sup>19</sup> Finally, in earlier population-based studies in Singapore, dietary soy was associated with lower serum estrogen,<sup>20</sup> reduced mammographic density,<sup>21</sup> and reduced breast cancer risk.<sup>22</sup> Soy isoflavones can inhibit free radical formation, reduce lipid per-

oxidation, and stimulate antioxidant enzymes in possible mechanistic pathways against breast carcinogenesis.<sup>23</sup>

## Conclusion

In conclusion, a concerted effort between the medical and scientific communities is needed to control cancer in postmenopausal women. While scientists continue to investigate activation pathways in drug development efforts to prevent and treat cancer, physicians who care for middle-aged and elderly women should continue to recommend cancer screening—especially for women at risk—and promote a healthy lifestyle that reduces obesity through increased physical activity and decreased caloric intake. As the chemopreventive properties of various nutrients are established, physicians should advise patients appropriately about the consumption of beneficial foods and dietary supplements.

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### Disclosure

Drs Koh and Lee indicate they have nothing to disclose.

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# Menopause and the Asian woman

## Is she different from women of other ethnicities?

• Foo-Hoe Loh, MBBS, MMed, FRCOG, FAMS

*"East is East, and West is West, and never the twain shall meet..."*

Rudyard Kipling

### Is this true of the menopause?

Menopause may be a universal biological phenomenon, but the individual experience of the menopause is a varied, multifaceted, multidimensional reality for women from different parts of the world. How a woman perceives and responds to the menopause is colored by her culture and her views on aging and sexuality. As with most biological phenomena, differences that we observe may have their origins in differing genetics interacting with lifestyle, culture, and other factors as yet undefined. Our approach to the manage-

ment of menopause must necessarily be guided by a sensitive understanding of these differences.

Stereotypically, the Western woman faces the menopause with dread, fearing the attendant decline of feminine allure so important in a youth-oriented society. In contrast, the Asian woman, living in a culture that venerates the elderly, would welcome the phase in which she no longer has to bear the discomfort of menstruation, and she acquires an enhanced status within the family. Yet this can be a rather simplistic generalization. It does not do justice to the wide spectrum of differences that exist even within the same culture.

Asia has more than half of the world's population. It embraces many different cultures ranging from East Asians in the Far East, to the South Asians in the Indian subcontinent, to the Middle Eastern cultures in western Asia. This is a vast and diverse spectrum of population, and hence no sin-

gle description will be able to typify the term "Asian."

For the purpose of this report, we shall focus our attention on the populations from 2 Asian groups: the East Asian populations such as the Chinese, Japanese, and Koreans, and the South Asian populations such as the Indians and Pakistanis. I shall draw heavily from data in our Singapore study.<sup>1</sup>

Singapore has a unique population of different ethnicities and cultures—Chinese, Indians, and Malays—living in close proximity on one small island. It is a melting pot where lifestyles and diets share more similarities than differences. This allows for a comparison of the different ethnic groups and cultures living in a common physical environment. Although Singapore cannot be truly representative of Asia, it may be considered a microcosm of modern, urban Asia.

### The Asian experience of menopause

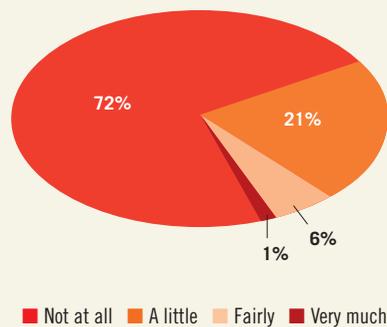
It is commonly believed that Asian women have a lower prevalence of menopausal symptoms than Western women. A survey of some of the epidemiological studies conducted in the different regions in Asia shows this to be generally true, with a few exceptions.<sup>2</sup> Our population-based Singapore study

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**FIGURE 1**

### Overall Disturbance by Menopausal Symptoms

Singapore Women Aged 45 to 60 Years



Loh FH, et al. *Maturitas*. 2005;52:169-180.

of 1000 Chinese, Malay, and Indian women aged 45 to 60 years noted that, overall, just 7% of the women were significantly bothered by any of the symptoms of menopause (FIGURE 1).

This is particularly true when we consider only classical vasomotor symptoms, such as hot flushes. Most studies conducted among Asian menopausal women demonstrate a prevalence of significant hot flushes of 10% to 20%,<sup>3,4</sup> while the prevalence of the same symptoms in Western women was 30% to 50%.<sup>5,6</sup> The SWAN study (Study of Women's Health Across the Nation)<sup>7</sup> in a US cohort confirmed this observation, noting that Chinese and Japanese women were far less likely to report significant symptoms than their Caucasian and African American counterparts.

However, several important points must be highlighted:

**1)** The stage of menopausal transition—rather than ethnic difference—is probably the most important determinant of the risk of experiencing the classical symptoms such as the hot flush. The perimenopausal woman is most likely to experience hot flushes, but this will resolve gradually, and most women will not be bothered by them after the fifth year of menopause.<sup>1</sup>

**2)** Within the Asian populations, there is a diverse range of experiences.

Indians are more likely to experience menopausal symptoms than are Chinese. Even among the East Asians, Chinese women appear to be more symptomatic than the Japanese.<sup>8</sup>

**3)** Nonvasomotor symptoms are more prevalent in Asian women than are vasomotor symptoms. Asian women experience fewer hot flushes than Western menopausal women; the most prevalent symptoms noted by Asian women are body and joint aches. This is a fairly consistent finding among most studies conducted in Asian populations. Other important symptoms which rank highly in Asian populations include sleeplessness and lethargy.

**4)** It may be difficult to distinguish between differences due to cultural or ethnic influences and those that reflect socioeconomic disparity. As a dramatic example, it is possible to imagine that an affluent woman entering the menopause would be more likely to be disturbed by menopausal symptoms than an impoverished woman for whom menopausal symptoms are a trivial concern compared with obtaining shelter and food. An interesting Chinese study noted that highly educated urban professionals were more symptomatic than rural women farmers.<sup>9</sup> Our Singapore study did not find differences in the risk of experiencing menopausal symptoms among the different economic and educational strata. But it may be that the gulf between the upper and lower socioeconomic strata in the Singaporean population is not as wide as that between an urban professional and a rural farmer in China!

### Diet and menopausal symptoms

Food selection and preparation are typical cultural influences on health. The Japanese diet is famously high in isoflavones in the form of soy products. Whether this alone accounts for the rather low symptom rate seen among Japanese menopausal women is debatable. Clinical

studies on soy supplementation have had rather mixed results to date.

Our Singapore study did not find any association between high dietary soy intake and reduced vasomotor symptoms.<sup>1</sup> Neither did the SWAN study,<sup>7</sup> which found no association between the consumption of soy isoflavones and rates of vasomotor symptoms. However, this may be a dose effect: median intake of isoflavones in the SWAN study was well below the average intake of more than 20 mg/d among Japanese living in Japan, which may be a difficult level for many women to achieve.<sup>10</sup>

### Cultural views of the menopause

Culture is an entity which is difficult to define in scientific terms. It can mean different things to different people. For our purpose, culture embodies not just the set of values but also particular diets and lifestyles that a cultural group embraces.

No culture exists in isolation. Given the ease of communication and intercontinental travel today, populations are constantly interacting. This fluid state of cultural evolution means constant modifications of dietary, lifestyle, and even reproductive choices. Hence, what we describe as true today may no longer be valid within the next decade.

For the moment, it can be asserted that the majority of Asian women in Asia embrace the menopause with stoic and tranquil acceptance, treating it as another milestone in the progression of life. Indeed, the term used in Chinese is simply "a change in life phase." Hence, most Asian women look upon the problems that accompany the onset of menopause as an inevitable part of aging to be embraced, rather than struggled against.

It is not easy to conduct a good study on cultural aspects of menopause, as many of the nuances may be lost in translation. It is also important

to understand that attitudes and beliefs can be modified by education, and it may not be easy to attribute what we observe as simply a cultural trait or a result of the education that a woman has received.

We found that Chinese, Malay, and Indian women residing in Singapore generally viewed the menopause positively. However, there is a significant correlation between education and belief. Women of higher educational levels are more willing to accept that there may be medical conditions associated with the menopause that require medical attention. Conversely, women of lower educational levels are more inclined to believe that menopause is a completely natural event for which it would be pointless to seek any medical attention.

It is somewhat surprising to read in the SWAN study<sup>11</sup> that Asian women residing in the United States viewed menopause less positively than their Western counterparts. The effect of acculturation is an interesting phenomenon which deserves greater study.

### The biological difference

Can the different menopausal experiences of women in different ethnic groups be explained simply by their cultural differences, or is this a difference in physiology?

There are indeed differences in the endocrine changes during midlife between the different ethnic groups. The SWAN study noted that Chinese and Japanese women have lower estradiol levels across the midlife transition compared with Caucasian and African American women. However, corresponding follicle-stimulating hormone (FSH) levels were not different between Asians and Caucasians.<sup>12</sup> The SWAN study also noted that only changes in annual FSH concentrations, when measured longitudinally, were correlated with the prevalence and frequency of vasomotor symptoms.<sup>13</sup> Evidently, we

have not elucidated all the parameters involved in the equation.

### Sexuality and the Asian menopausal woman

Asian women are thought to have a more conservative attitude toward sexuality than their Western counterparts. However, aside from ethnicity and culture, there are many other important parameters which influence sexuality: education, affluence, and geographic location. This is probably true of all cultures.

Our Singapore study suggests that the large majority of women in their forties and fifties are still sexually active, with gradually lower levels of sexual activity over the years. Menopause does have a negative impact on their level of sexual activity, but it is not a unique factor. Women in higher income households and of higher educational levels are more likely to be sexually active.

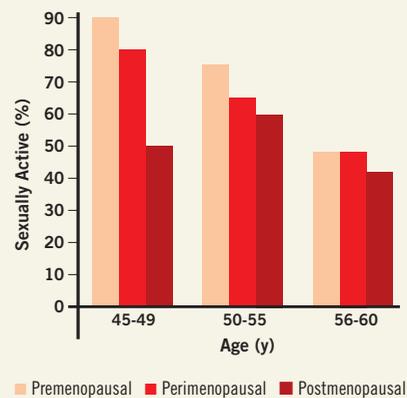
The onset of menopause has a greater effect on sexuality when the final menses occurs at a relatively young age. For example, a woman who becomes menopausal in her forties is far less likely to remain sexually active compared with her premenopausal counterparts (53% vs 89%). For women aged 55 to 60 years, there is less difference in sexual activity between postmenopausal and premenopausal woman (44% vs 50%) (FIGURE 2).

The changes that accompany menopause, such as vaginal dryness and loss of sexual desire, are common in Asian and Western women. However, Asian women tend to regard these changes as less important. A large proportion of these women do not appear to be too disturbed by these changes. One survey conducted by a pharmaceutical company in 7 countries in Europe (4200 women) and 5 countries in Asia (1000 women) noted that the prevalence of sexual dysfunction, such as reduced sexual desire and painful sex, was high (>50%) on both continents.<sup>14</sup> However, 64% of Asian women did not feel that their reduced sex drive

FIGURE 2

### Impact of Menopausal Status on Sexual Activity

Singapore Women Aged 45 to 60 Years



Loh FH, et al. *Maturitas*. 2005;52:169-180.

lowered their self-confidence, and more than 90% accepted the belief that reduced sexual desire is a natural consequence of getting old.

### The Asian woman's response to menopausal symptoms

Faced with significant symptoms, what do Asian women do about them?

Hormone therapy (HT) is not a popular first-line option. The Asian arm of the multinational survey described above noted that approximately 43% of the women in Asia have a negative view of HT. Among the Asian countries, the Taiwanese and Thais have the highest rates of women who had ever used HT (25% to 30%) and current HT users (9% to 12%), but even these are low by most Western standards. China has the lowest rates of women who had ever used HT (2%) and who currently use HT (1%).<sup>13</sup>

The Japan Nurses Health Study noted that among their postmenopausal women, the rate of ever having used HT was just over 10%, while the current HT user rate was about 5%.<sup>15</sup> HT use among Singaporean postmenopausal women is very similar, with 12% having ever used HT and 5% currently using it. Over half of these women used HT for less than 1 year.<sup>1</sup>

Herbal and traditional therapies are popular options, and approximately one third of menopausal women have either tried them or are currently using them for their symptoms.<sup>14</sup>

Anecdotally, many said they would also try various lifestyle modifications, such as dietary adjustments (avoiding spicy foods) and exercises (tai chi, yoga) to overcome many of the disturbances of menopause. To them, this is appropriate, as menopause is not an “illness,” and many feel that taking medication for a natural life milestone is not totally appropriate.

It is pertinent to highlight that the most prevalent symptom in many Asian populations is body ache and shoulder stiffness. Aside from cultural and economic considerations, given that HT is not particularly efficacious against such symptoms, it may be understandable that the use of HT is not especially high in Asian countries.

## The future of menopause management in Asian women

The current buzzword in HT is “individualization” of treatment. For a variety of reasons, this is particularly true for Asian women.

Many of the available HT preparations are researched and manufactured in the United States and Europe, where many of the drug trials are conducted. However, we are beginning to recognize that the results of these drug trials may not be simply extrapolated to Asian populations.

### Dose

One basic but important consideration is dosing. The correct dose for a Western woman may not be correct for an Asian woman for a myriad of reasons. Asian women are generally of smaller build and have lower body mass indices. Their metabolism and pharmacokinetics may be quite different from their Western counterparts. There is growing interest in having many of the clinical

trials primarily conducted in the United States and Europe, also conducted in the Asia Pacific region as well, so as to facilitate understanding of the effects of these drugs in Asian women.

About 5 years ago in Singapore, it was noticed that the (then) conventional dose of continuous combined preparations was fraught with many side effects for our patients. Many patients complained of breast tenderness, bloating, and a high rate of breakthrough bleeding. We performed a randomized trial to compare the conventional dose (estradiol, 2 mg, plus norethisterone, 1 mg) with a (then) low-dose preparation (estradiol, 1 mg, plus norethisterone, 0.5 mg) in Chinese women in Singapore. The results demonstrated that the lower dose is just as efficacious, with fewer side effects such as breast pain, and a much better bleeding profile.<sup>16</sup>

This finding is consistent with that of larger trials, such as the HOPE trial<sup>17</sup> performed in the United States using conjugated equine estrogens and medroxyprogesterone acetate, as well as the more recently published Pan-Asian menopause study conducted across 11 Asian countries.<sup>18</sup>

The current trend is toward regimens with even lower doses, and we await with great excitement the effects of these agents on the Asian population.

### Differences in disease patterns

Asian women have a rather different disease risk profile from their Western counterparts, though rapid modernization and changing dietary/lifestyle patterns in Asia are causing a convergence of these disease patterns. Of importance are the risks of breast cancer, osteoporosis, and venous thromboembolism.

Venous thromboembolism is an uncommon but important complication of HT. There is some evidence to suggest that Asians may have a lower risk of deep vein thrombosis,<sup>19</sup> and their risk of thrombosis while on hor-

mones and selective estrogen-receptor modulators may also be lower.<sup>20</sup>

Hence, the global risk-benefit equation of HT currently postulated for Western populations after the publication of the Women’s Health Initiative (WHI) may not be the same for Asian women. Given current sentiments about HT, I doubt anyone has sufficient courage or resources to embark on a trial similar to WHI in an Asian population. However, given what we do know now after numerous analyses of the pitfalls of the WHI, it would be interesting to postulate how a similar trial with an improved design and patient selection would emerge in an Asian population.

### The role of herbal and other traditional alternatives

The information we have today suggests that many of the herbal alternatives do not have greater efficacy than placebo. Although some clinical trials of soy and black cohosh used for the treatment of hot flushes demonstrated a positive effect,<sup>21</sup> many others have failed to confirm this finding.<sup>22,23</sup> Nevertheless, interest in these traditional options remains strong in the Asia Pacific and in many Western countries, where herbal alternatives may be viewed as more “natural.”

There is much that we do not know about these traditional options, and their value is being investigated. What better place than Asia to conduct these trials? The challenge for investigators will be to demonstrate efficacy and safety of these options with sufficiently robust data from well-designed trials. The next few decades will be an exciting time to witness the new developments in this field.

### Conclusion

The experience of menopause is very different across cultures. Asian women are probably less likely to experience the hot flushes and night sweats typical of a Western menopausal woman,

but they are more likely to have somatic symptoms of body and joint aches. Asian women are likely to embrace this change stoically and are less inclined to seek treatment in general or use HT in particular. They have rather different health risks and the global risk-benefit calculation for HT may also be different for Asian women.

As in all other fields of medicine, it is important that we adopt a culturally appropriate approach to the management of the menopause.

#### Disclosure

Dr Loh indicates he has nothing to disclose.

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# Osteoporosis in Asian populations

• L K H Koh, MD, FRCP

Osteoporosis is a public health problem that is projected to escalate to epidemic proportions in Asia over the next 30 to 50 years, at which time more than half of all hip fractures worldwide will occur in Asia.<sup>1,2</sup> Recent research into the genetics, epidemiology, diagnosis, and treatment of osteoporosis in Asia has revealed

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many similarities to and some differences from studies carried out in the West. This review highlights some of the issues of this worldwide problem from an Asian perspective.

## Fracture rate variation by geography and development

Reports on hip fracture rates from various Asian countries show that fracture rates vary considerably among populations.

• Taiwan,<sup>3</sup> Singapore,<sup>4</sup> and Hong Kong<sup>5</sup> reported high age-adjusted hip fracture rates of 400 to 500 fractures per 100,000 women, which approached

rates in Caucasian populations.

• In Japan, rates of 200 to more than 300 hip fractures per 100,000 women were reported.<sup>6</sup>

• In Malaysia and Thailand,<sup>5</sup> hip fracture rates of between 200 to 250 fractures per 100,000 women were found.

• In Korea and China, hip fracture incidence of approximately 100 fractures per 100,000 women was reported; this rate was observed to have increased over a short time interval.<sup>7,8</sup>

Hip fracture rates in Asia have increased compared with rates seen in past decades. Hip fracture rates increased 4- to 5-fold over a period of 30 years in Singapore<sup>4</sup> and Hong Kong,<sup>9</sup> and 1.5-fold over a 15-year period in Japan.<sup>6</sup> As in the West,<sup>10</sup> the real reasons for such trends remain obscure, but these trends seem to parallel urbanization and lifestyle changes. As Thailand

and Malaysia urbanize, rate increases are expected to be comparable to those experienced by Singapore and Hong Kong. Within the same country, ethnic differences in hip fracture rates have also been reported,<sup>4,5</sup> but the reasons for this remain undetermined.

The mortality, morbidity, and social burden of hip fractures in Asian countries are similar to those in the West. After a hip fracture, 20% of patients die within 2 years, 33% remain ambulant without aids, 40% are ambulant with aids, and 10% are wheelchair- or bed-bound.<sup>11</sup> More than 90% of survivors of hip fracture are discharged to their own homes.

Interestingly, the epidemiology of vertebral fractures in Asia appears to differ from that of hip fractures. Although rates of hip fracture among the Japanese and Chinese are lower than the rates in Caucasians, the prevalence of vertebral fractures among these populations are more similar.<sup>12,13</sup>

## The genetics of osteoporosis in Asians

There has been a proliferation of research on the genetics of osteoporosis in Asians that examines a host of candidate genes. There appear to be differences in the genotypic makeup of Asian and Caucasian populations, with differing effects on bone density and fractures.

Gene polymorphisms reportedly associated with fractures include those of the estrogen receptor<sup>14</sup> and transforming growth factor  $\beta$ -1.<sup>15</sup> The pattern of gene polymorphisms of the vitamin D receptor, particularly the high b allele frequency by Bsm1 restriction fragment length polymorphism, are similar among Koreans,<sup>16</sup> Japanese,<sup>17</sup> Chinese,<sup>18</sup> and Thais,<sup>19</sup> but different from Caucasians.

The correlation of vitamin D receptor polymorphisms with BMD appears weaker than the correlation of gene polymorphisms associated with frac-

ture. Polymorphisms may affect BMD via gene/environment relationships, resulting in increased bone loss,<sup>20</sup> differences in gastrointestinal handling of dietary calcium,<sup>19</sup> and response to estrogen.<sup>21</sup> Other polymorphisms related to BMD include those of the estrogen receptor,<sup>14</sup> parathyroid hormone receptor,<sup>22</sup> calcium-sensing receptor,<sup>23</sup> low-density lipoprotein receptor-related protein 5,<sup>24</sup> parathyroid gene,<sup>23</sup> osteocalcin gene,<sup>25</sup> collagen type I alpha 1 gene,<sup>26</sup> calcitonin gene,<sup>27</sup> transforming growth factor  $\beta$ -1,<sup>28</sup> and peroxisome proliferator-activated receptor- $\beta$  gene.<sup>29</sup> The clinical applicability of these findings remains to be determined, but they underscore the polygenic nature of osteoporosis, with no single gene of predominant importance.

## Diagnosis

Large scale epidemiological trials documenting the relation of BMD to fracture risk in Asians are lacking, and most data are extrapolated from studies in Caucasian populations.<sup>30</sup> However, smaller studies have shown that fracture risk is increased in Asians with lower BMDs.<sup>31,32</sup>

In general, BMD is lower in Asians than in Caucasians, possibly due to the generally smaller body size of Asians.<sup>33,34</sup> Yet hip fracture rates among Asians remain lower than among Caucasians. It has been suggested that shorter hip axis lengths among Asians may be protective.<sup>35,36</sup> In Singapore, ethnic differences in hip axis length, rather than BMD, mirrored the ethnic differences in hip fracture incidence.<sup>37</sup> Recent data also show that there are ethnic differences in fracture risk given any peripheral BMD T score, with Asians experiencing fewer fractures than Caucasians and Hispanics.<sup>38</sup> Despite this, there are no data to suggest that the threshold for osteoporosis in Asians should be anything other than the generally accepted T score of  $-2.5$  standard deviations below the young adult mean. However, the Japa-

nese have adopted a cutoff of 70% of the young adult mean.<sup>39</sup>

Several Asian studies have shown that biochemical markers of bone turnover may be useful in monitoring response to therapy. Bone turnover markers were suppressed with antiresorptive agents, and changes in these markers were inversely related to changes in BMD.<sup>40,41</sup>

Although an osteoporosis epidemic is anticipated in many Asian countries, diagnostic dual energy x-ray absorptiometry (DXA) devices to measure BMD are relatively scarce, inaccessible, and expensive, and they are usually located in population centers. To facilitate case-finding for osteoporosis and enhance the judicious and appropriate use of BMD measurement, several clinical screening tools have been developed. The Osteoporosis Self-Assessment Tool for Asians (OSTA)<sup>42</sup> has been validated in Asian as well as in Caucasian populations.<sup>43,44</sup> This simple screening tool appears to be robust and effective.

## Osteoporosis and fracture risk factors

Several studies in Asian populations, most of which have been relatively small, have reported on a range of risk factors for osteoporosis<sup>45</sup> and fractures.<sup>46,47</sup> The risk factors for hip fractures—which were similar to risk factors in Caucasian populations<sup>48,49</sup>—included a history of fracture, sedative use,<sup>46,47</sup> taller stature, and physical inactivity.<sup>46</sup> Other important risk factors for hip fractures in Asian populations include a history of stroke, excessive alcohol intake,<sup>46,47</sup> dietary calcium intake less than 500 mg/d, 2 or more falls in the past year, and the use of thyroid medication.<sup>46</sup> Calcium intake seems to have a relatively greater impact on osteoporosis and fractures among Asians compared with Caucasians,<sup>45-47</sup> possibly related to the generally lower calcium intake of Asians throughout their lives.

Japanese, whether native or Ameri-

can, seem to fall less often than do Caucasians,<sup>50,51</sup> and this may be related to better musculoskeletal functioning.<sup>52</sup> The risk factors for falls among Asians, such as various visual and motor incapacities,<sup>53,54</sup> appear similar to those in Caucasians.<sup>55</sup>

## The importance of lifestyle factors

The largest of the epidemiological studies relating dietary calcium to osteoporosis among Asians suggests that calcium intake below 500 mg daily is associated with increased risk for hip fracture.<sup>46</sup> A calcium balance study in elderly Japanese suggested that the daily calcium requirement for women is about 800 mg, and for men, 700 mg.<sup>56</sup> Calcium supplementation appears to be beneficial in Asians<sup>57</sup>; milk is one effective dietary calcium source.<sup>58</sup>

Apart from an apparent difference in fracture risk for a given bone density as described above,<sup>38</sup> several nutritional reasons may partially explain the lower fracture rates in Asians than in Caucasians, despite low mean dietary calcium intake in Asian populations (350 to 500 mg/d).<sup>46</sup> Asian women may absorb calcium more efficiently, particularly when dietary calcium intake is low<sup>59</sup>; this may be a result of common vitamin D receptor polymorphisms among Asians.<sup>19</sup> The effects of low dietary calcium may also be offset by an abundance of other nutrients commonly found in Asian diets. Observational studies have demonstrated skeletal benefits of consuming dietary phytoestrogens, of which soy-based products are a major source,<sup>60</sup> fish,<sup>61</sup> and fermented soybeans, a rich source of vitamin K2.<sup>62</sup> However, omnivorous diets seem to be more beneficial for bone health than vegetarian or lacto-vegetarian diets.<sup>63</sup>

The importance of vitamin D as a controllable nutritional risk factor for osteoporosis and musculoskeletal function has recently re-emerged.

Vitamin D deficiency (defined as serum 25-hydroxyvitamin D [25(OH)D] <25 nmol/L) is common in the Middle East, India, China, Japan, and Korea.<sup>64,65</sup> Vitamin D insufficiency (defined as 25(OH)D <75 nmol/L) is widespread throughout Asia and the world. This phenomenon may be related to socio-cultural factors, as well as misperceptions about vitamin D.<sup>64,66</sup>

Reduced physical activity is associated with increased risk for hip fracture.<sup>46</sup> A fall intervention program was shown to reduce the risk for falls<sup>67</sup> and presumably may help reduce fractures.

## Treatment

Early studies of therapy for osteoporosis in Asians, conducted primarily in Japan, centered on the effectiveness of the vitamin D analog alfacalcidol.<sup>68,69</sup> Direct comparisons of alfacalcidol with other therapies such as hormone replacement<sup>70</sup> and the bisphosphonate alendronate<sup>40</sup> have shown the superior efficacy of the latter drugs.

As in Caucasian menopausal populations, hormone therapy (HT),<sup>71</sup> alendronate,<sup>72</sup> risedronate,<sup>73</sup> raloxifene,<sup>74</sup> and intermittent parathyroid hormone injections<sup>75</sup> were effective in maintaining or improving bone density in Asian populations. Although Asians demonstrated a similar BMD response to alendronate as Caucasians did,<sup>76</sup> dose-ranging studies among Japanese have suggested that a lower dose of alendronate (5 mg daily<sup>77</sup> and 35 mg weekly<sup>78</sup>) and risedronate (2.5 mg daily<sup>79</sup> and 17.5 mg weekly<sup>80</sup>) may be as effective in improving BMD as higher doses were.

Studies demonstrating the anti-fracture efficacy of osteoporosis drugs in Asian patients have been reported recently. Alendronate, 5 mg daily, reduced vertebral fractures compared with alfacalcidol.<sup>81</sup> Risedronate, 2.5 mg daily, was better than cyclical etidronate, 200 mg daily, for 2 weeks of 12-week cycles in reducing vertebral fractures in sub-group analysis.<sup>82</sup> Raloxifene reduced

new vertebral fractures in a post hoc analysis combining 2 trials.<sup>83</sup> HT, cyclical etidronate, and subcutaneous calcitonin appeared to be more effective than placebo in reducing new vertebral fractures.<sup>84</sup>

## Conclusions

Many aspects of osteoporosis in Asians appear similar to those in Caucasians, but several interesting differences have emerged, notably differences in fracture risk at a given BMD and the seemingly larger role of dietary factors in fracture risk among Asians. A nuanced understanding of critical differences among women by ethnicity may lead to refinements in the strategies to manage osteoporosis within the Asian context.

## Disclosure

Dr Koh indicates he has nothing to disclose.

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