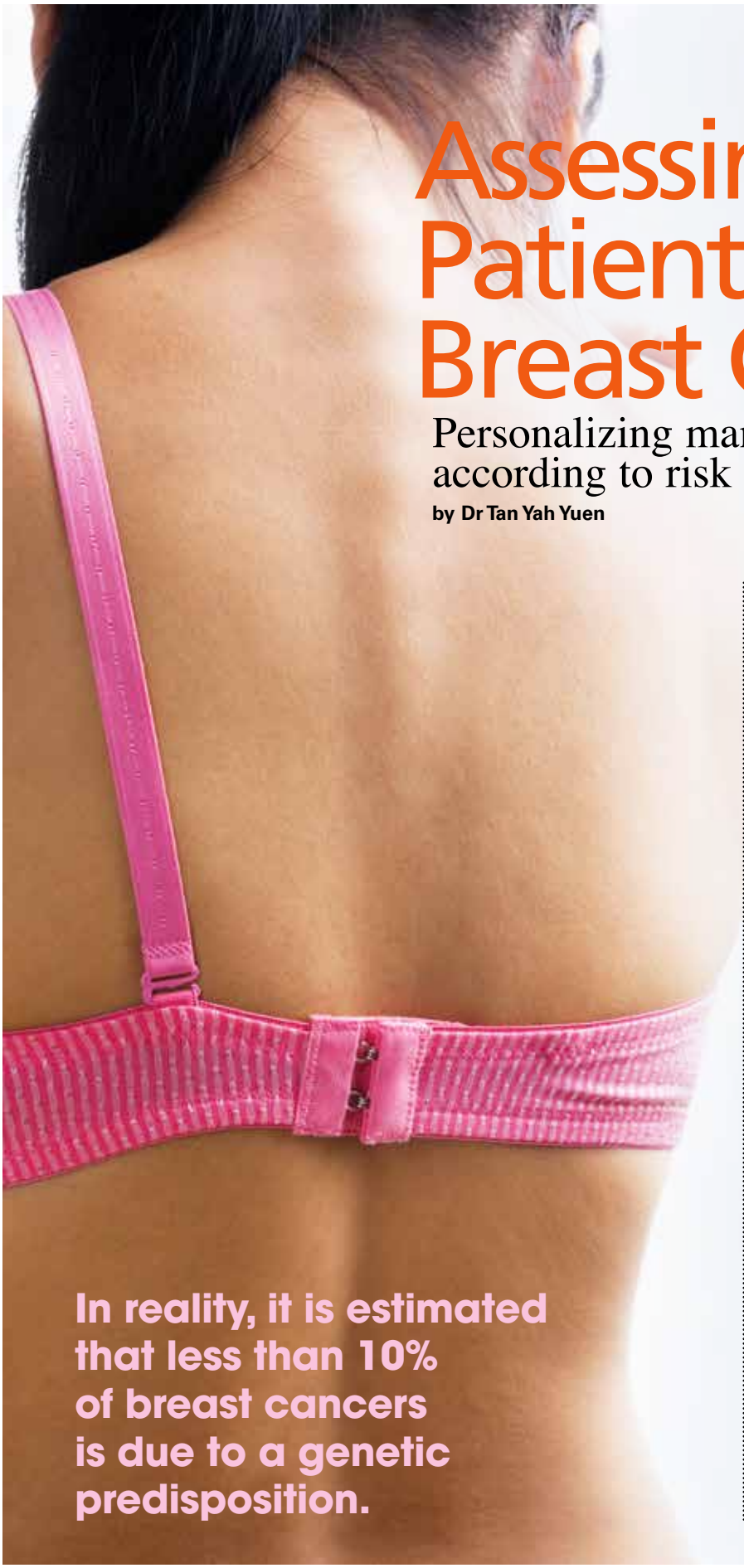

Assessing Your Patient's Risk of Breast Cancer

Personalizing management according to risk

by Dr Tan Yah Yuen

Breast cancer is the most commonly diagnosed cancer among women in Singapore and many Western countries. In recent years, there has been increased awareness of breast cancer partly due to the higher incidence, and partly due to the widespread publicity created by celebrity star Angelina Jolie. Angelina Jolie was diagnosed to have an increased lifetime risk of breast and ovarian cancer because she inherited the BRCA gene mutation. She made headlines when she opted for prophylactic surgery to have her breasts and ovaries removed to lower her cancer risk.

In reality, it is estimated that less than 10% of breast cancers is due to a genetic predisposition. With more women in the general population developing breast cancer, how then does one distinguish between a possible genetic association and sporadic breast cancer development? Can we calculate a woman's risk of breast cancer and then develop strategies for prevention based on different risk thresholds?

In reality, it is estimated that less than 10% of breast cancers is due to a genetic predisposition.

Can it be genetic breast cancer? Does your patient need genetic testing?

BRCA 1 and 2 gene mutations are responsible for the majority of genetic breast cancer. In addition to an elevated breast cancer risk, mutation carriers also carry a long term elevated risk of ovarian cancer.

***Table 1.* Referral Screening Tool. A referral for genetic testing is recommended if there are ≥2 checks. (from Genet Med. 2009;11:783-9)**

Risk Factor	Breast Cancer at Age ≤ 50 y	Ovarian Cancer at Any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on the same side of the family		
Male breast cancer at any age in any relative		
Jewish ancestry		

A BRCA gene mutation is associated with young age at breast cancer diagnosis (<50 years of age), bilateral breast cancer, presence of both breasts and ovarian cancer, breast cancer in a male family member, multiple cases of breast cancer in the family and Ashkenazi Jewish ethnicity.

There are several scoring systems that can be used to predict the likelihood of a possible BRCA genetic mutation in a woman who presents with a personal or family history of breast and/or ovarian cancer[1]. These include the Ontario Family History Assessment Tool[2], Manchester Scoring System[3], Referral Screening Tool[4], Pedigree Assessment Tool[5], and Family History Screen[6]. The Referral Screening Tool is one of the easiest to use **[Table 1].**

Genetic testing can be complicated and intensive pre-test and post-test counseling is required to ensure the woman fully understands the implications, benefits and limitations of genetic testing. For example, a positive genetic test does not mean a certainty of cancer development and a negative test does not mean the woman will never develop cancer. A woman should be referred to a medical oncologist for discussion of the usefulness of genetic testing in her specific circumstances.

How do I calculate my patient's risk of breast cancer?

There are several statistical models that may be used to calculate a woman's risk of breast cancer, taking into account factors such as age, menstrual history, age of live births, previous breast biopsy results and family history. These models are all based on databases in the West. There is currently no statistical model based on Asian populations in an Asian country.

The International Breast Intervention Study (IBIS) risk tool or Tyrer-Cuzick model is a validated tool based on data from the IBIS in the UK[7]. It can be accessed at http://ibis.ikonopedia.com.

After entering the data, the model calculates the 10 year as well as lifetime risk of breast cancer, with a comparison to the population risk for the same period. The model includes long term risk estimation in women with a history of lobular neoplasia, atypical ductal hyperplasia and BRCA gene mutation. This model should be used if the above circumstances are present.

The other statistical model, the National Cancer Institute Breast Cancer Risk Assessment Tool, is derived from USA data. It can be accessed at http://www.cancer.gov/bcrisktool/Default.aspx.

This model is based on the older Gail model version and does not take into account a prior history of ductal carcinoma in situ, lobular neoplasia or BRCA gene mutation, or family history beyond first degree relatives. There is however, a selection for ethnicity (Asian American – Chinese, Japanese, Filipino and Others) based on data from these sub-populations in the USA. The 5 year and lifetime risk of breast cancer is calculated after inputting the necessary information.

Screening with imaging should begin 5-10 years earlier than the youngest family member with breast cancer. For women with diagnosed BRCA mutations, screening should begin even earlier at age 25.

What do I do with the woman with an increased risk of breast cancer?

Depending on the quantum of elevated risk, different strategies may be discussed and employed.

Enhanced Surveillance Screening

Screening with imaging should begin 5-10 years earlier than the youngest family member with breast cancer. For women with diagnosed BRCA mutations, screening should begin even earlier at age 25.

MRI screening for breast cancer has been found to be more sensitive in detecting invasive cancer especially in young BRCA mutation carriers[8] where radiation at a young age should be minimized. Women who may benefit from MRI screening include any of the following[9]:

- BRCA gene mutation carriers
- An untested first degree relative of a BRCA gene mutation carrier
- History of therapeutic chest wall radiation between the ages of 10 and 30 years
- Life time risk of ≥20-25% of breast cancer (according to the risk assessment tools above).

MRI of the breasts is performed with IV contrast, and detection of breast cancer is enabled by examining the abnormal enhancement pattern in the breast tissue. As breast enhancement can be affected by the hormonal changes during the menstrual cycle, MRI of the breasts should ideally be timed on day 7-15 of the menstrual cycle and this will reduce false positives. MRI is recommended annually to begin 10 years prior to the youngest family member with breast cancer, but not younger than age 25 years[10]. MRI screening should be integrated with other breast imaging modalities such as mammogram and ultrasound of the breasts.

Annual screening mammogram should also be performed at women at increased risk of breast cancer, starting at 10 years earlier than the youngest family member with breast cancer, but not earlier than age 30 years[10]. As young women often have dense breasts which lowers the sensitivity of mammogram screening, the addition of tomosynthesis (a form of multi-slice mammogram imaging) may improve cancer detection rates[11] although the radiation dose is significantly increased. Tomosynthesis is available is most specialized radiological facilities and tertiary hospital settings in Singapore.

In practice, MRI of the breasts is expensive and may not be affordable on a routine screening basis. In our local context, the addition of routine breast ultrasound to annual mammogram screening may be more practical if cost is a concern, and ultrasound can be useful for detecting small cancers in dense breasts[12]. However women with significantly higher breast cancer risk should consider the addition of MRI screening to annual mammography.

Chemoprevention

Chemoprevention is defined as "the use of pharmacologic or natural agents that inhibit the development of invasive breast cancer either by blocking the DNA damage that initiates carcinogenesis or by arresting or reversing the progression of premalignant cells in which such damage has already occurred"[13]. Drugs such as Tamoxifen (a selective estrogen receptor modulator) and aromatase inhibitors (Anastrazole, Exemestane) have been shown to reduce breast cancer incidence by about 50% in women with elevated risk of ≥1.66% in 5 years based on the National Cancer Institute Breast Cancer Risk Assessment Tool (see above) or an equivalent measure[14]. These are the same drugs that are being given as adjuvant endocrine therapy in women who are being treated for breast cancer. Hence chemoprevention is only indicated for women with an increased risk of breast cancer, defined here as at least ≥1.66% in 5 years. There is no evidence that chemoprevention reduces breast cancer incidence in women at average risk.

While the concept of chemoprevention is attractive, these drugs are not without risk of adverse events. The significant events include and are not limited to weight gain, venous thromboembolism, pulmonary embolism, endometrial cancer and osteoporosis. Due to these risks, most of our Asian female population with increased breast cancer risk often decline chemoprevention. Women at elevated risk who are keen to discuss chemopreventive strategies should be referred to a medical oncologist for further discussion regarding benefits, limitations and risks.

Risk Reducing Surgery

Bilateral risk reducing mastectomy has been found to reduce the risk of breast cancer by at least 90% in women with elevated risk including BRCA gene mutation carriers[15]. In recent years, advances in immediate breast reconstruction techniques have made this option more attractive although there is some concern regarding the overzealous uptake of contralateral mastectomy especially in the USA, amongst women who have been diagnosed with probable sporadic unilateral breast cancer.

Women with a newly diagnosed breast cancer

As mentioned earlier, genetic breast cancer constitutes <10% of all newly diagnosed breast cancer cases. The majority of women with newly diagnosed breast cancer do not have a cancer gene or significant family history, therefore the estimated risk of a second breast cancer in the opposite breast is 0.5% per annum[16]. The use of adjuvant endocrine therapies such as Tamoxifen and aromatase inhibitors for the treatment of the index cancer will further reduce this risk over the years[17]. Hence in the majority of these women, contralateral prophylactic mastectomy is not necessary.

While a woman may instinctively desire bilateral mastectomy at the point of diagnosis of a unilateral breast cancer, this is often a knee-jerk reaction and she should receive adequate counseling and have a "cooling off" period before making her decision, when she is less emotionally vulnerable[18]. Most importantly, she has to understand that a contralateral mastectomy: a) does not improve cure rates of the current cancer b) does not reduce the amount of treatments necessary to treat the current cancer c) is not 100% protective against cancer development in the opposite breast d) occasionally may delay the treatment for the current cancer due to increased risk of surgical complications[19].

While breast cancer may not be absolutely prevented, there are many avenues to reduce the long term risk depending on a woman's specific risk factors.

Case Example:

A 48 year old lady visits you and she is concerned about her breast cancer risk. Her maternal grandmother had breast cancer at age 68, and her maternal aunt was also diagnosed with breast cancer at 55. She has 2 children and she was 32 when she gave birth to her elder son. She has no previous history of breast biopsy.

1. Using the Referral Screening Tool, she has 2 checks so she should be referred to a medical oncologist to discuss genetic cancer screening.

2. Using the IBIS risk calculation tool, assuming the patient does not have any BRCA cancer gene, the estimated 10 year risk is 3.1% (compared to average population risk at 2.5%) and her lifetime risk is 14.3% (compared to average population risk at 11.8%). This is probably an overestimation for our Asian population, where the average population lifetime risk of breast cancer is about 5%. However it does give an idea of the magnitude of increased risk this patient has compared to the average woman.

3. Based on these calculations,

- **the patient should be referred to a medical oncologist for counseling on genetic testing**
- **she should institute lifestyle modifications and reduce her alcohol intake**
- **she does not require enhanced surveillance screening, chemoprevention or risk reducing surgery**
- **however, if she undergoes genetic testing and is found to have the BRCA 1 or BRCA 2 gene mutation, her 10 year and lifetime risk of breast cancer becomes 23-33% and 65-72% respectively. This elevated risk means she should have enhanced surveillance screening and consider chemoprevention and /or bilateral risk reducing mastectomy.**

Women with elevated breast cancer risk with or without a diagnosed breast cancer

In contrast, the risk of a contralateral breast cancer in women with a known BRCA gene mutation is about 2-3% per annum[20]. Bilateral risk reducing mastectomy should be considered in these high risk women, as well as women with an unknown gene status but with a strong family history.

In women with BRCA gene mutations, there is also an elevated lifetime risk of ovarian cancer. In these patients, risk reducing salpingo-oophorectomy reduces breast cancer risk by 50% and ovarian cancer risk by 80%[21].

Table 2. ***Summary of associations between foods/nutrients and breast cancer risk among females, by menopausal status. (from CA Cancer J Clin 2008;58:347-371).***

Food or Nutrient	Effect Among Premenopausal Women	Effect Among Postmenopausal Women	Level of Evidence Based Upon Selected References
Alcohol	5% to 10% increase in risk per 10 grams of alcohol per day	5% to 10% increase in risk per 10 grams of alcohol per day	Pooled analysis of 6 prospective studies
Total fat	No association	Equivocal findings	Observational cohort, Nurses' Health Study; randomized study, Women's Health Initiative, pooled analysis of 8 studies: observational cohort, AARP Diet and Health Study
Type of fat	Inconsistent associations overall, trend of increased risk with increased animal fat intake	Weak positive association for saturated fat intake; mixed results for unsaturated fats	Observational cohort, Nurses' Health Study; randomized study, Women's Health Initiative, pooled analysis of 8 studies: observational cohort, AARP Diet and Health Study
Total carbohydrate	No association	No association	Observational cohort, Nurses' Health Study
Carbohydrate quality (glycemic index and glycemic load)	No association	No association	Observational cohorts, Cancer Prevention Study II, Nurses' Health Studyand Women's Health Study
Fiber	No association	No association	Observational cohort, Nurses' Health Study
Red meat	Inconsistent association overall; increased risk with increased meat consumption maybe restricted to hormone-sensitive breast malignancies	Inconsistent association overall	Observational cohort, Nurses' Health Study and UK Women's Health Study; pooled analysis of 8 prospective studies
Dairy/milk	No association	No association	Pooled analysis of 8 prospective studies; observational cohort, Nurses Health Study
Fruits and vegetables	No association	No association	Pooled analysis of 8 prospective studies
Soy/ phytoestrogens	-30% reduced risk among those reported highest intakes	-20% to 25% reduced risk among those reporting the highest intakes	Meta-analysis; review
Caffeine	No association	No association	Observational cohort, Swedish Mammography Screening
Vitamin D	Reduced risk among women with high serum vitamin D	Possible reduced risk among women with high plasma vitamin D	Observational cohort, Nurses' Health Study
Vitamins E, A, and C	Weak association for decreased risk with increased intake, which may be modified among women with a family history of breast cancer	No association	Observational cohort, Nurses' Health Study
Folic acid	No association, but increased intake may moderate risk of excess alcohol consumption	No association, but increased intake may reduced excess breast cancer risk due to alcohol consumption	Observational cohort, Nurses' Health Study
Carotenoids	Trend favoring risk reduction among highest quintiles of carotenoid consumption, may be variable by carotenoid class	Trend favoring risk reduction among highest quintiles of carotenoid consumption and serum carotenoid levels; may be variable by carotenoid class	Observational cohort, Nurses' Health Study

Micronutrients, specifically carotenoids, exhibit a great deal of interindividual variation, in their absorption, metabolism, excretion.[86, 103]

In risk reducing mastectomy, the woman may choose to preserve the nipple/areolar complex, which yields superior aesthetic results. Immediate reconstruction is commonly performed using retropectoral breast implants, latissimus dorsi (LD) flap, transverse rectus abdominis myocutaneous (TRAM) flap or the deep inferior epigastric perforator (DIEP) flap. The choice of type of reconstruction suitable is made taking into account breast size, stage of cancer (if present), effect of any further adjuvant treatment such as radiotherapy on the reconstruction, the patient's own desire, body habitus and risk factors such as obesity, smoking history and diabetes mellitus.

Lifestyle modifications

A common sense approach should be adopted towards lifestyle modifications in reducing breast cancer risk. Healthy eating is recommended, although there is no clear evidence that specific dietary components can effectively reduce breast cancer risk. In particular,

alcohol consumption has been found to be a consistent risk factor so women at elevated risk should be counseled to reduce or moderate their intake **[see Table 2]**. Hormonal replacement therapy after menopause may be considered in women with significant symptoms, but should be discouraged beyond 5 years of use. The combined pill increases breast cancer risk after 5 years of use, whereas the estrogen-only pill increases breast cancer risk after a longer period of 10-15 years of use[22-23]. Upon discontinuation of hormone therapy, risk progressively reduces to normal after 5 years[24].

Women should maintain a healthy body mass index especially after menopause. BMI in excess of 31 resulted in a doubling of risk of postmenopausal breast cancer[25], especially for hormone receptor positive breast cancer[26]. A weight gain of more than 25kg since age 18 years is associated with a 50% increased risk of invasive breast cancer[27]. While observational studies have suggested that higher levels of physical activity may reduce the rates of breast cancer, this may be related to its role in controlling weight gain rather than due to the physical exercise itself. In general, all persons are encouraged to engage in at least 30 minutes of moderate to vigorous intensity physical activity on at least 5 days per week[28].

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Conclusion

Many women are concerned about their risk of breast cancer, especially when a family member or even colleague is diagnosed. Most breast cancers are sporadic in nature, and <10% are attributed to a hereditary predisposition. Several online tools are available to assist the physician in decision making: whether the woman should be referred for genetic testing, calculation of the absolute risk of breast cancer, and whether specific strategies such as enhanced surveillance, lifestyle modifications, referral to a medical oncologist for chemoprevention or to a surgeon for discussion of risk reducing surgery is necessary. While breast cancer may not be absolutely prevented, there are many avenues to reduce the long term risk depending on a woman's specific risk factors. MG

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