

placebo. The results were subsequently published in 2004, clearly demonstrating a significant reduction in both invasive carcinoma (26%) and DCIS (70%), confirming the results of the NSABP P-1 study. The reduction in breast cancer risk was only seen in oestrogen receptor positive disease. Again the reduction in breast cancer incidence associated with Tamoxifen was independent of age. Tamoxifen was associated with a 2.4 fold increase in endometrial carcinoma and a two-fold increase in thromboembolic events. Compliance with Tamoxifen for all studies was high, between 70-80%.

Tamoxifen vs Raloxifene

In 2006 the initial results from the STAR trial were released⁴. The study enrolled 19,747 postmenopausal women at risk of breast cancer who were randomized to Raloxifene 60 mg or Tamoxifen 20 mg once daily for five years. The trial evaluated the efficacy and safety of Tamoxifen compared with Raloxifene. The results of the trial demonstrated that the number of invasive breast cancers was statistically equivalent (167 in the Raloxifene group compared with 163 in the Tamoxifen group). Both drugs reduced the risk of invasive breast cancer by around 50%. Raloxifene was associated with fewer cases of endometrial cancer compared with Tamoxifen (23 versus 36) and a 29% reduction in cases of thromboembolism. Raloxifene did not impact the incidence LCIS or DCIS whereas Tamoxifen was associated in a reduction in these non-invasive breast cancers by approximately 50%. There were no differences in strokes, heart attacks or bone fractures between Tamoxifen and Raloxifene.

At present, neither Tamoxifen nor Raloxifene are registered for use as chemoprevention agents in breast cancer by the Therapeutic Goods Administration in Australia. Tamoxifen is classed as a carcinogen by the North American FDA due to its endometrial cancer risk. Despite its similar efficacy to Tamoxifen in reducing invasive breast cancer, Raloxifene has no impact in reducing the incidence of pre-invasive cancer which is of clinical importance.

Tamoxifen vs aromatase inhibitors

More recently, the results of large international multi-institutional studies have confirmed superiority of adjuvant aromatase inhibitors over Tamoxifen for postmenopausal women with oestrogen receptor positive breast cancer in reducing breast cancer recurrence. Side effects appear to be fewer with the aromatase inhibitors, with no excess of gynaecological (including endometrial cancer) or thromboembolic events, but an increase in fracture risk and joint symptoms does occur. Based on the results of these trials, the IBIS II trial has recently commenced with the aim of comparing the safety and efficacy of Tamoxifen 20 mg daily and Arimidex (Anastrozole) 20 mg daily for five years for women at risk of breast cancer due to family history or histological risk factors such as DCIS or a atypical ductal/lobular hyperplasia. The primary end point is breast cancer incidence and major efforts are also being directed at minimising any fracture risk. The trial aims to recruit approximately 10,000 women worldwide. To date over 4,300 women have entered the trial.

For more information

Treating physicians or women interested in participating in the IBIS II trial may contact Ms Wendy Schwerdt, South Australian IBIS II study coordinator on 08 8222 2017 or www.ibis-trials.org/index.php

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References available upon request to genetics@cancersa.org.au

Resource update

Booklet

Information for women considering preventive mastectomy because of a strong family history of breast cancer—developed by Hereditary Cancer Clinic, Prince of Wales Hospital and the Centre for Genetics Education (NSW).

This booklet provides useful information about breast surgery and breast reconstruction. It also provides information about decision making and support options. Available from **Cancer Council Helpline 13 11 20**.

Web based

If you would like access to up to date cancer genetics information and resources from one easy site, visit the **Cancer Genetics Resource Directory** at www.cancer.org.au/aboutcancer/Geneticsdirectory.htm

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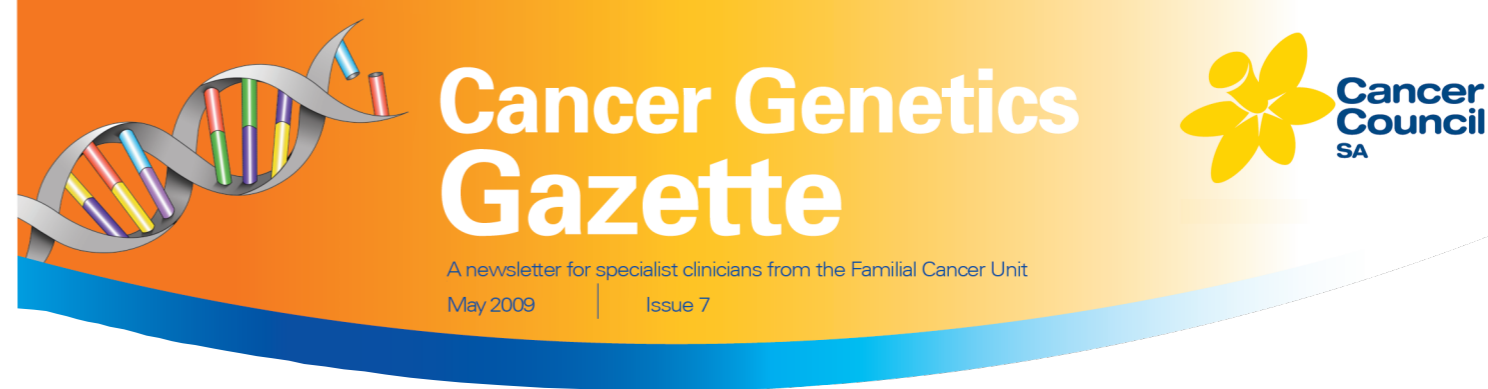
Feedback?

If you have any feedback from this edition or suggestions for future topics please email Kirsty Stallard, Cancer Genetics Education Project Officer at genetics@cancersa.org.au

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Welcome to the 1st edition of the Cancer Genetics Gazette for 2009. We have three feature articles in this edition. The first article, by Dr Nicola Poplawski, Clinical Geneticist at the Familial Cancer Unit, provides important information about **Familial gastric cancer**. The second article, by breast surgeon Dr Melissa Bochner gives an update on the use of **MRI for breast cancer screening in breast cancer gene carriers**. Finally, breast and endocrine surgeon Dr James Kollias presents the current status of **Chemoprevention and breast cancer**. We hope you find this bumper edition useful and informative.

Familial gastric cancer— an update

The incidence of gastric cancer varies geographically; incidence is highest in Eastern Asia (including Japan and China), some regions of South America, and in Eastern Europe and lowest in North America, Northern Europe, most areas of Africa and South East Asia, and Australasia.¹ Of note, there is a high incidence of diffuse gastric cancer in New Zealand Maori families.

Each year almost 2,000 Australians are diagnosed with gastric cancer. The risk to age 75 is approximately 1 in 110 for Australian males and 1 in 250 for Australian females (1 in 55 and 1 in 130, respectively, to age 85) with a median age at diagnosis around 72 years for males and 76 years for females. Gastric cancer rarely occurs before age 40; in 2005 42 gastric cancers were diagnosed in people less than 40 years old, representing only 2.3% of all gastric cancer diagnoses.

Most gastric cancers are sporadic and reflect the gradual accumulation of genetic errors with age, combined with environmental factors, age and chance. Risk factors for sporadic gastric cancer include *Helicobacter pylori* infection, smoking and dietary factors (low in fruit and vegetables, high in salted smoked, cured and/or pickled foods, high in heavily grilled or barbecued meat and fish). Approximately 10% of gastric cancers show familial clustering suggestive of an inherited genetic predisposition. The genetic factors involved in most familial gastric cancers are poorly understood, although specific mutations have been identified in a small subset of families.

More than 90% of gastric cancers are adenocarcinoma. The Lauren system divides gastric adenocarcinoma into two major histological variants; type I or intestinal-type, and type II or diffuse-type (aka linitis plastica or signet ring adenocarcinoma). Pure intestinal-type is the most common (~50%), followed by pure diffuse-type (35–45%) and cancers with a mixed phenotype (5–15%). The Lauren system is used widely as the two histologic subtypes have clinically relevant differences:

- intestinal type gastric cancer is associated with most of the environmental risk factors (see above) and is not usually associated with a familial history of cancer. When there is a family history of cancer, other non-gastric cancers tend to dominate the history. The most common implicated genes are those associated with
 - Lynch syndrome (MLH1, MSH2, MSH6 and PMS2 genes), where colorectal, endometrial and ovarian cancers dominate the family history
 - Li-Fraumeni syndrome (TP53 gene), where sarcoma, breast and brain cancers dominate
 - Familial adenomatous polyposis (APC gene), where colorectal adenomas and colorectal cancer dominate the family history
 - Peutz-Jeghers syndrome (STK11 gene), where hamartomatous polyps of the small intestine and mucocutaneous pigmentation dominate the family history
 - BRCA2-associated hereditary breast and ovarian cancer (BRCA2 gene), where breast and ovarian cancer dominate the family history
- diffuse type gastric cancer is not strongly associated with environmental or dietary risk factors, occurs more often in relatively young patients (mean 40 years; range 14–85 years)² and is commonly associated with a family history of gastric cancer. Germline (inherited) mutations of the E-cadherin (CDH1) gene are detected in up to 50% of families with a history of diffuse gastric cancer in multiple family members (i.e. have familial diffuse gastric cancer).³

CDH1 and hereditary diffuse gastric cancer

Germline mutations in the CDH1 gene cause hereditary diffuse gastric cancer (HDGC), an autosomal dominant susceptibility to both diffuse gastric cancer and lobular breast cancer. There may be an increased risk of signet ring carcinoma of the colon, although this remains unclear. CDH1 encodes the protein E-cadherin and is the only gene known to be associated with HDGC. Although E-cadherin is ubiquitously expressed it is not known why germline CDH1 mutations predispose to diffuse gastric cancer and lobular breast cancer but not other epithelial malignancies.

HDGC is highly penetrant. In CDH1 mutation carriers the estimated cumulative risk of advanced gastric cancer to age 80 years is 67% for men and 83% for women.⁴ Early data suggests that for women who carry a germline CDH1 mutation, the risk of lobular breast cancer to age 80 years may be as high as 39%.⁴

Management of CDH1 mutation carriers (male and female) is focused on either intense surveillance for early detection and treatment of gastric cancer or prophylactic gastrectomy. Optimal management is controversial because the effectiveness of endoscopy in detecting early gastric cancer lesions is unknown; on the other hand, there is considerable long-term morbidity associated with prophylactic gastrectomy.

Women who carry CDH1 mutations should have more intensive breast cancer surveillance, probably beginning at a younger age, than women at population risk. However the optimal time to commence breast cancer screening is unclear because of lack of data; the 39% risk figure quoted above is based on 7 breast cancers diagnosed at a mean age of 53 years (range 39–64 years) in 11 HDGC families which included 235 females (and 241 males).⁴ The optimal breast screening modality to use in HDGC families is also unclear. Mammography is not particularly effective at detecting the lobular subtype of breast cancer but there is no data addressing the effectiveness of screening by MRI and/or ultrasound in the HDGC setting. Given these controversies it is strongly recommended that individuals with HDGC be managed in a multidisciplinary setting by a group of expert colleagues.

Mutation testing in familial gastric cancer

Intestinal-type gastric cancer can occur as a component of other familial cancer syndromes where non-gastric cancers predominate (see above). Mutation testing of the appropriate gene(s) should be considered where there is a family history suggestive of one of these syndromes.⁹

Familial diffuse gastric cancer usually presents as the predominant feature of an autosomal dominant gastric cancer pedigree with no striking family history of other cancers (except, perhaps, lobular breast cancer). Genetic testing in the CDH1 gene should be considered in families where

- a familial mutation in the CDH1 gene has been identified, or
- a patient has diffuse gastric cancer diagnosed under the age of 40 years, or
- a patient has lobular breast cancer and a first or second degree relative with diffuse gastric cancer (or vice versa), with one of diagnoses being under the age of 50 years, or
- a patient has diffuse gastric cancer (any age) and a first, second, or third degree relative with diffuse gastric cancer (any age).

How to access genetic testing for familial gastric cancer

The Familial Cancer Unit offers genetic counselling and genetic testing for familial gastric cancer in South Australia. Familial Cancer Clinics are held at most major public hospitals in Adelaide and in some regional centres (Port Augusta and Mount Gambier).

Referral letters should be addressed to Dr Graeme Suthers or Dr Nicola Poplawski and sent to the:
Familial Cancer Unit

SA Pathology, Women's and Children's Hospital
72 King William Road, North Adelaide SA 5006
t 08 8161 6995 f 08 8161 7984
e cywhs.famcancer@health.sa.gov.au

Please include the patient's particulars (name, date of birth, address, contact number) and as much information as you have about their personal and family history of cancer.

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References available upon request to genetics@cancersa.org.au

The use of magnetic resonance imaging (MRI) for breast cancer screening in breast cancer gene carriers

Women who carry a mutation in BRCA1 or BRCA2 are at increased risk of developing breast cancer, with a risk of up to 40% before the age of 50¹. The aim of population based mammographic breast screening programs is to reduce morbidity and mortality from breast cancer and its treatments by detecting cancers at an early stage². However the accuracy of mammography is reduced in premenopausal women who are more likely to have high breast density. In addition, tumours in young women who are gene carriers may have a faster doubling time than sporadic cancers and be more likely to present as interval cancers, even in women undergoing yearly mammography¹.

A number of studies have examined the impact of adding yearly breast MRI to mammography in screening high risk women. Warner et al³ performed a meta-analysis of 10 non-randomised prospective studies, reporting sensitivity and specificity of 39% and 95% for mammography, 77% and 86% for MRI and 94% and 77% for mammography and MRI together. It is important to note that while these studies show a marked increase in sensitivity for breast cancer diagnosis when MRI is added to mammography, resulting improvements in morbidity or mortality have not been demonstrated.

One of the advantages of MRI is that it does not rely on ionising radiation, which is a concern when contemplating early onset of screening for high risk women, in whom interval examinations may be useful. The images are independent of breast density, which may account for the increased sensitivity when compared with mammography.

A recent study by Bigenwald⁴ has suggested that while diagnostic sensitivity for invasive cancer for mammography compared with MRI improves as breast density decreases, this may not be true for DCIS, and that MRI has greater sensitivity for DCIS, even in women with low breast density.

There are a number of disadvantages to breast MRI. The investigation requires an intravenous injection of contrast and many women find the procedure uncomfortable because of the prone positioning. Some women with claustrophobia are unable to tolerate MRI at all, while the size of the coil may exclude some women with large breasts or with a high BMI. Because MRI has a lower specificity than mammography, the investigation of false positives may lead to psychological distress and unnecessary open biopsies in some women.

The use of MRI for breast cancer screening requires specialized equipment and protocols. A 1.5 Tesla machine with a dedicated breast coil is required. Intravenous gadolinium is used, and images are generated at 90 seconds, 3 minutes, 4.5 minutes and 7 minutes after injection. Both

Indications for Medicare rebate for screening breast MRI

Magnetic Resonance Imaging performed under the professional supervision of an eligible provider at an eligible location where the patient is referred by a specialist or by a consultant physician and where:

- a dedicated breast coil is used
- the request for scan identifies that the woman is less than 50 years of age
- the request for scan identifies either
 - that the patient is at high risk of developing breast cancer due to one of the following
 - 3 or more first or second degree relatives on the same side of the family diagnosed with breast or ovarian cancer
 - 2 or more first or second degree relatives on the same side of the family diagnosed with breast or ovarian cancer, including any of the following features
 - bilateral breast cancer
 - onset of breast cancer before the age of 40 years
 - onset of ovarian cancer before the age of 50 years
 - breast and ovarian cancer in one relative
 - Ashkenazi Jewish ancestry
 - breast cancer in a male relative
 - 1 first or second degree relative diagnosed with breast cancer at age 45 years or younger, plus another first or second degree relative on the same side of the family with bone or soft tissue sarcoma at age 45 years or younger or
 - that genetic testing has identified the presence of a high risk breast cancer gene mutation.

Scan of both breasts for

- detection of cancer (R)

Note: Benefits are payable on one occasion only in any 12 month period

kinetics of contrast enhancement as well as morphological appearance of lesions are important in determining the likelihood of malignancy. Lesions measuring less than 5 mm may require repeat MRI in three to six months. Radiologists reporting breast MRI are generally specialist breast radiologists who have undergone specific MRI training and who have the skills to correlate findings with mammography and ultrasound (US). Many lesions detected on breast MRI may be subsequently localised and biopsied with dedicated breast US, although MRI guided biopsy is available in some centres⁵.

In early 2009 a Medicare rebate became available for MRI screening for breast cancer for women under 50 who are known

carriers of a high risk breast cancer gene mutation or who have a strong family history of breast and/or ovarian cancer (see box). Eligible women must be referred by a specialist.

Screening breast MRI is now also routinely offered through the **Breast/ovarian high risk clinics** held at the Royal Adelaide Hospital and The Queen Elizabeth Hospital. Women with a proven BRCA mutation or at high genetic risk of breast and/or ovarian cancer are eligible to attend.

For more information about the clinics and referral process please contact the Breast/ovarian high risk clinic coordinators:

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References available upon request to genetics@cancersa.org.au

Chemoprevention and breast cancer—current status

The first Tamoxifen trials

Chemoprevention for breast cancer was first described in 1998 when the results of the National Surgical Adjuvant Breast and Bowel Project Prevention-1 (NSABP P-1) study of Tamoxifen versus placebo were published¹. In this trial, 13,388 women at increased risk of breast cancer, principally due to a family history of the disease, were randomized to receive Tamoxifen 20 mg or placebo for five years. The results demonstrated that Tamoxifen significantly reduced the risk of invasive breast cancer and DCIS by approximately 50%. The risk reduction applied to women of all age groups. This came at a cost of a slightly increased risk in endometrial cancer, stroke, pulmonary embolism and deep venous thrombosis. These side effects occurred mainly in women 50 years of age or older.

However the results of two subsequent randomised trials from Milan and the Royal Marsden Hospital failed to confirm the benefit of Tamoxifen in reducing breast cancer risk in susceptible women^{2,3}. Both trials were smaller than NSABP P-1 with fewer person years follow-up and fewer events.

The second largest international breast cancer prevention trial (IBIS study) was similar in design to the NSABP P-1 study. IBIS randomised 7,000 women who had at least a four-fold increased risk of developing breast cancer to either Tamoxifen 20 mg daily or