THE INTEGRATED, MULTIDISCIPLINARY CLINIC: A NEW MODEL FOR THE ONGOING MANAGEMENT OF WOMEN AT HIGH GENETIC RISK FOR BREAST AND OVARIAN CANCER

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Abstract

An important minority of Australian women have a strong hereditary predisposition for the development of breast and/or ovarian cancer. Evidence-based cancer risk reduction strategies for this group are complex and need to be tailored to individuals and refined as new evidence emerges. In Australia, risk management services for these women are largely unidisciplinary. Here we describe the development, feasibility and cancer and screening outcomes for the first two years of an Australian multidisciplinary Risk Management Clinic (RMC). Data on screening test results and risk-reducing surgery were collected prospectively using standardised forms. Data on clinical and genetic characteristics were collected by medical record review. A total of 98.8 years of follow-up were available on the 92 clients. The average age of clients was 36 years and 20 (22%) carried a documented mutation in *BRCA1* or *BRCA2*. One interval breast cancer had been diagnosed and screening investigations resulted in three investigational operative gynaecological procedures for non-malignant disease. Forty-three (47%) clients were participating in at least one research project. It is feasible in the Australian setting to run a multidisciplinary risk management clinic, with integrated clinical research programs, within the setting of a Family Cancer Centre.

In Australia, approximately one in 12 women will develop breast cancer and one in 100 will develop ovarian cancer by the age of 75.[1] For an important minority of Australian women, the risk is much higher because they have a strong family history of breast and/or ovarian cancer.[2] Two important genes have been identified that are associated with an increased risk for breast and ovarian cancer, namely *BRCA1* and *BRCA2*.[3] A woman who has inherited a mutation in *BRCA1* or *BRCA2* has a 60% to 80% risk of developing breast cancer[4,5] and a 15% to 66% risk of ovarian cancer by age 75 years.[6,7] There is also growing evidence to suggest that individuals with a *BRCA1* or *BRCA2* mutation have an increased risk for other cancers.[7,8] Other much rarer gene mutations known to cause hereditary breast cancer are p53 (Li-Fraumeni Syndrome) and PTEN (Cowden's Syndrome).

Family Cancer Centres were established to provide genetic counselling and testing to individuals with a strong family history of cancer. These centres operate in most capital cities, many also providing an outreach service to rural centres. (www.nbcc.org.au/pages/info/risk/genserv.htm) These clinics have traditionally focused on assessment of risk rather than ongoing management of cancer risk. Risk assessment involves several steps including: reviewing family history (attempts are made to confirm all reported cancers), estimation of the client's risk for cancer development and genetic counselling and testing (if appropriate). For those ultimately determined to be at high risk, a discussion of risk management strategies is usually encompassed in the consultation. This includes both surveillance and prevention strategies (Tables 1 and 2).[9-16] National guidelines exist for the management of high-risk women (Table 2)[16] however, because this is a rapidly moving field, best practice may alter several times before updated guidelines are published.

After initial recommendations are made, ongoing multidisciplinary risk management is not generally undertaken as part of Family Cancer Centre activities, rather individuals are required to make their own arrangements for cancer surveillance, usually through individual private specialists. Consumers have identified this as problematic for a number of reasons. It can be difficult to identify breast and gynaecological specialists with particular expertise in the field of genetics and who are likely to be motivated to keep up with the large and emerging literature in this highly specialised area. Having to attend multiple different specialists and diagnostic facilities on different days and in different locations is inconvenient and results in a focus on ill health rather than wellness, which is inappropriate for women who are at risk but in fact have no personal history of cancer. There is a perception that a non-multidisciplinary, decentralised arrangement for cancer risk management may also result in a suboptimal level of coordination of care between the specialties and limited opportunities to participate in relevant clinical research. In Europe and North America the need for centralised multidisciplinary care of *BRCA1* and *BRCA2* mutation carriers and other women at very high genetic risk has been recognised and has resulted in recommendations for, and the development of, such clinics.[17]

Here we describe the initiation, feasibility and outcomes from the first two years of a centralised multidisciplinary Breast and Ovarian Cancer Risk Management Clinic (RMC), initiated at the Peter MacCallum Cancer Centre in September 2001 for women at very high risk for breast and/or ovarian cancer. To our knowledge this is currently the first clinic of its type in Australia.

Table 1: Breast and ovarian cancer risk reduction strategies for BRCA1 and BRCA2 mutation carriers

INTERVENTION OR STRATEGY	EFFECT ON BREAST CANCER RISK	EFFECT ON OVARIAN CANCER RISK
Risk-reducing salpingo-oophorectomy	53% reduction[9,10]	96% reduction[9,10]
Risk-reducing Mastectomy	90% reduction[11]	-
Oral Contraceptive Pill	20% increase*[12]	0-50% reduction[13,14]
Tubal Sterilisation	-	63%* reduction[15]

*Effect only seen in *BRCA1* mutation carriers

Table 2: Surveillance guidelines for women at high risk of breast and/or ovarian cancer

BREAST CANCER	OVARIAN CANCER
• Maintain breast awareness. • Attend for 6-12 monthly clinical breast examination. • Report to GP promptly with any breast changes. • Attend for annual mammographic screening (and possibly ultrasound) commencing at age 40, and consider starting five years earlier than the youngest breast cancer case in the family, whichever is earlier.	• Discuss with woman that there are no data which conclusively demonstrate that surveillance has a favorable impact on either stage at diagnosis or the mortality of ovarian cancer in women at risk. • Unnecessary intervention can sometimes result after a false positive test and that interval cancers can develop between tests. • Attend for annual transvaginal ultrasonography (TVUS), preferably with colour flow Doppler, commencing at age 25-30 years, or at least five years younger than the age of diagnosis of the youngest ovarian cancer case in the family, whichever is earlier. • Annual CA125 measurement may be appropriate as an additional screening test after menopause (timed with TVUS).

From : Familial aspects of cancer: a guide to clinical practice, NHMRC, 1999[16]

Methods

Risk management clinic

With the aim of providing a centralised, multi-disciplinary, peer-reviewed specialist service for the ongoing management of women at high risk of breast and/ or ovarian cancer, the Familial Cancer Centre at the Peter MacCallum Cancer Centre, initiated a RMC in September 2001. An additional aim of the clinic was to enable such women access to clinical research programs. Breast surgeons, gynaecologic oncologists, medical oncologists with expertise in clinical cancer genetics and a clinical nurse specialist attend each monthly clinic. Dietetic, social work and psychology services are available on call. All women attending the clinic have no personal history of breast or ovarian cancer, but must have at least an estimated 30% risk for breast cancer to age 75 years. The 1999 NHMRC surveillance guidelines (Table 2) are used as a guide to determine the surveillance strategies to be used for each individual.

Women who require surveillance investigations, such as mammograms, transvaginal ultrasounds or CA125 testing, have these carried out on the morning of their visit to the RMC. During a multidisciplinary pre-clinic meeting all test results are reviewed and each individual is discussed with respect to any new information from the literature that might alter their personal risk management plan and any new research protocols for which they may be eligible.

Women are seen by the appropriate specialists in the afternoon clinic. Most women see the breast surgeon at every visit for a clinical breast examination, who also reviews their mammogram result (if done). Women who are undergoing gynaecological surveillance or who wish to discuss risk-reducing salpingo-oophorectomy or use of hormonal contraceptive or hormone replacement therapy also see the gynaecologic oncologist. When there is new information from the literature that might impact on a woman's personal risk and/or management plan, she is seen by the medical oncologist.

Long hand progress notes are written in the clinic, but there is also systematic recording by clinicians of key pieces of information on specially designed data forms, with a plan to ultimately enter those data into a prospective database. The clinical nurse specialist is essential to the functioning of the clinic. She coordinates appointments for surveillance investigations and the specialist consultations. In addition, she carries a pager and is the first point of contact for women who have concerns about symptoms that might occur between clinic visits. She assesses the symptomatology over the phone and contacts the most appropriate specialist to set up an urgent review appointment.

Data collection

Data on frequency and results of screening tests, such as breast examination, mammograms, CA125 tests and transvaginal ultrasound, were documented in each woman's medical record using the standardised forms which constitute the bulk of each woman's history (and are supplemented where necessary by hand-written notes). A copy of the pathology reports and surgical notes were obtained from the respective surgeon's records and filed with the patient's record. These data, along with relevant clinical and genetic data, were extracted from the records.

Statistical analysis

Descriptive statistics were used including the calculation of median and mean scores.

Results

Characteristics of attendees

To October 2003 there were 92 women, with no personal history of cancer, who had attended the RMC. All women had had at least one risk assessment consultation prior to attending the RMC. The median number of RMC visits was two (range one to four), representing a total of 98.8 client years of follow-up for the 92 women. The mean age of attendees at their first visit was 36 years (range 19 to 65 years). All women have at least an estimated 30% life-time risk for the development of breast cancer and 58 also have a substantially increased risk for ovarian cancer. Sixty-nine (75%) of the women live within the Melbourne metropolitan region, the remaining 23 (25%) travel to the clinic from rural centres. Three women have ceased attending the clinic; one because she moved interstate, one has had a subsequent negative predictive mutation test and is now considered at average cancer risk and one woman from a rural centre has subsequently developed breast cancer and is pursuing follow up with her local specialists.

Prior to their first appointment in the RMC, five patients had undergone risk-reducing salpingo-oophorectomy. One of these women has a known *BRCA2* mutation, while for the others genetic testing is not currently possible. An additional woman who had not undergone genetic testing had previously had a unilateral salpingo-oophorectomy for investigation of cystic changes. No woman had undergone a risk-reducing mastectomy or tubal sterilisation for risk-reducing purposes

prior to her first RMC attendance, although two women had previously had tubal sterilisation for contraceptive reasons.

Genetic testing

Twenty women of the 92 attendees (22%) are known to carry a genetic mutation, six in *BRCA1* and 14 in *BRCA2*. One additional Jewish woman has had testing and was found to be negative for mutations associated with Ashkenazi Jewish families. Three attendees are yet to decide whether they wish to undergo predictive testing for family specific mutations in either *BRCA1* or *BRCA2*. An additional patient is also yet to decide about testing for a p53 mutation, which has been found in an affected member of her family. There are 67 (73%) high-risk women who attend the clinic who have not been able to undergo genetic testing for *BRCA1* or *BRCA2*. For 40 (43%) of these, another cancer-affected relative in the family has been tested but no mutation was found. This does not necessarily mean there is no underlying gene mutation in the family. It may mean that a mutation in *BRCA1* or *BRCA2* was missed (because testing is not 100% sensitive) or that there is an underlying mutation in another gene for which testing is not available, so in such cases the woman is still considered high risk. Eleven (12%) women have not been able to undergo testing because there is no living cancer-affected family member available for testing. In general, initial genetic testing in a family is commenced with a person who has had cancer, to maximise the chance of finding a genetic mutation. A person who has no history of cancer may be unaffected because they have not inherited a gene mutation that may have been found had an affected family member been tested. For five (5%) women, testing is not yet available because the cancer-affected individuals in their family have declined or are still thinking about mutation testing. For the remaining eleven women for whom a genetic test has not yet been possible, testing has been carried out in their cancer-affected relatives, but results are currently pending.

Clinical events

Cancer surveillance

At all visits either the breast surgeon or the medical oncologist has performed a clinical breast examination. Sixty-four women have undergone either a baseline mammogram or are having regular mammographic screening. Three of the 94 mammograms carried out to date have been reported as abnormal requiring further investigation. Two women had an additional ultrasound that confirmed that the noted abnormalities were benign cysts. In one woman the initial mammogram showed two small nodules, thought to be benign, this was repeated at six months with no interval changes noted. An additional five women have significantly increased overall breast density for their age, therefore reducing the sensitivity of mammography. Ultrasounds have since been added to their surveillance regimen.

Currently 31 women are undergoing regular screening for ovarian cancer. Four of 59 transvaginal scans have been reported as abnormal. Two of these showed increased endometrial thickening in postmenopausal women, both of whom underwent subsequent investigative hysteroscopy and dilatation and curettage procedures, with no malignancy detected. One of the abnormal scans was in a premenopausal woman who was found to have an ovarian cystic mass with septations and who subsequently underwent an investigative laparoscopy with unilateral salpingo-oophorectomy (physiological follicles were diagnosed at surgery). The other abnormal scan was in a perimenopausal woman. It showed a cystic mass, probably arising from the ovary, with a single septation. This had resolved at an arranged repeat scan. In one perimenopausal and one post-menopausal woman, at least one ovary was not identified on ultrasound using either a trans-vaginal or trans-abdominal approach. None of the 60 serum CA 125 levels that have been assessed have been reported as abnormal, including those women who have had abnormalities noted on their transvaginal ultrasound.

Risk reducing surgery

Since their first visit to the RMC, four of the 31 women (13%) at increased risk for ovarian cancer, for whom risk reducing salpingo-oophorectomy has been recommended as an option, have undergone bilateral risk reducing salpingo-oophorectomy. One of these has a mutation in *BRCA1*, two have a *BRCA2* mutation and in one genetic testing has not been possible, but she is considered to be at very high risk for ovarian cancer because of her family history. No occult cancers were found at surgery, however one pathologist reported surface papillary changes in both ovaries for the woman without a BRCA mutation. No woman has undergone a bilateral risk reducing mastectomy.

New cancers

One 31-year-old woman has had an interval breast cancer diagnosed. Her surveillance recommendations had been for a clinical breast exam every six months and increased breast awareness. Mammography was planned to commence from the age of 35 years. The patient detected a small lump in her breast five months after her last clinic visit, at which time the clinical breast examination had been normal. The pathology after initial breast conservation surgery revealed an 11mm, axillary node negative, grade 2 tumour which was oestrogen receptor positive, progesterone receptor negative and strongly overexpressed HER2/neu on immunohistochemistry. She declined the recommended adjuvant systemic therapy and has subsequently been diagnosed with metastatic disease. Mutation testing had not previously been possible for this patient (because there was no living cancer affected individual in the family to test). The patient elected to have genetic testing at the time of her diagnosis but no mutation was identified in either *BRCA1* or *BRCA2*.

New information conveyed

Since the commencement of the clinic in September 2001, new data on genetic risk modifiers have been published.[9,10,12] These data and the implications they potentially have on women attending the clinic were discussed in detail at pre-clinic meetings. The clinicians have been able to relay the information to appropriate women and have assisted them, where necessary, in adjusting their ongoing personal risk management plans.

Participation in research

Since the clinic's inception three major research projects have been open for recruitment and participation offered to eligible women; a study comparing two methods of information to assist decision making about risk-reducing salpingo-oophorectomy, a cancer family cohort study ("KConFab") and a study of breast ductal lavage as a potential new risk refinement and breast cancer screening method. Forty three women are currently enrolled in at least one of these research studies. Future studies anticipated to soon also be available for women attending the RMC are the international chemoprevention study, IBIS II and a US Gynaecologic Oncology Group observational study of ovarian surveillance versus risk reducing salpingo-oophorectomy.

Discussion

The monthly RMC, a surveillance and management clinic for women at very high risk for breast and/or ovarian cancer,

commenced operation in September 2001 and has been running for two years. The multidisciplinary "one-stop shop" style of the clinic enables evidence-based, peer-reviewed, integrated specialist management of individuals and the opportunity to participate in research. Women attending the clinic anecdotally report high levels of satisfaction with this form of health care provision, the drop out rate is low and there is currently accrual of approximately three to four new women at each clinic. To date there has been one interval breast cancer and three surgical gynaecological interventions for abnormal ovarian screening results. Risk reducing mastectomy has not been used as a risk management strategy by any of these women to date, but risk-reducing salpingo-oophorectomy has been used by 13% of those to whom it has been recommended as an option.

Currently little is known about what cancer surveillance and management strategies are being undertaken by Australian women who have attended a Family Cancer Centre for a risk assessment consultation. Published data suggest reasonably high utilisation of breast screening but poor utilisation of ovarian screening, prior to the first visit to a Family Cancer Centre,[18,19] however there are no published studies regarding the subsequent screening habits of these women. We, in conjunction with many other Australian Family Cancer Centres, have recently conducted a large multicentre study addressing this question, which has shown that a large proportion of high-risk women do not follow screening guidelines recommended to them, often for logistical reasons (unpublished data).

We have demonstrated the feasibility of a multidisciplinary RMC running within the setting of a Family Cancer Centre. As the focus of breast cancer genetics moves away from merely categorising the risk level of women to actively attempting to reduce their risk of morbidity and mortality from breast and ovarian cancer, we anticipate that other Australian Family Cancer Centres may initiate similar clinical services.

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