



CANCER FORUM

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Clinical cancer genetics

OVERVIEW

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A new diagnosis of cancer has been made and – after the initial questions about staging and treatment have been tackled – the patient often asks “Does this mean my relatives are at increased risk of cancer?” The answer depends on a number of features: the specific type of cancer, the age at cancer diagnosis and the presence or absence of the same (or associated) cancers in other family members. This assessment can usually be left until treatment is well underway, but sometimes the diagnosis of a genetic susceptibility to cancer can have an immediate impact on the treatment options that can be offered.

The family history can be important for the care of both the patient and family at large and so the taking of a clear family history is not an option – it is an essential part of the care provided by every healthcare professional. When there is uncertainty about the significance of a family history of cancer, this is best addressed by referral to a familial cancer service. Familial cancer clinics are now an important component of contemporary multidisciplinary cancer care.

This issue of Cancer Forum provides an overview of the way in which familial cancer services operate. A general introduction to cancer susceptibility and genetic testing is provided by Judy Kirk, while Graeme Suthers tackles some of the complex issues around genetic testing and information management. The most commonly referred histories are those involving breast/ovarian cancer and bowel cancer, highlighted in articles written by Kathryn Field with Kelly-Anne Phillips and Barbara Leggett (respectively); management of the high-risk individual is addressed in detail. Paediatric malignancies may be involved in a variety of cancer predisposition syndromes, reviewed by Michael Field. Finally, advances in two relatively new areas (hereditary diffuse gastric cancer, discussed by Georgina Fenton) and familial haematological malignancy (discussed by Catherine Carmichael and Hamish Scott) highlight that the field of clinical cancer genetics is expanding.

THE ROLE OF FAMILIAL CANCER SERVICES

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Abstract

There is now an improved ability to detect people at high-risk of cancer through analysis of their family history and genetic testing. Advances in cancer screening, cancer surveillance and cancer prevention have accompanied this. It is important to identify individuals at high cancer risk so that these advances can be applied in their management. Equally important, is the identification of those not at high-risk, so that they are spared unnecessary cancer screening and concern. Risk assessment and genetic testing is available in Australia through familial cancer services. This article introduces the

Cancer is a genetic disease

Cancer is a genetic disease, associated with alterations (mutations) in genes that normally act to control cell growth, proliferation and DNA repair. These genetic mutations (genetic "hits") usually occur in somatic (tissue) cells over the course of a lifetime. In this way, cancer is usually due to a series of acquired mutations in genes that control cell growth, eventually allowing cells with these faults to grow in an uncontrolled fashion. Up to 95% of all cancers are caused by these somatic mutations in cancer-associated genes. Because they occur in somatic cells, they are not inherited.

However, some rare families have an inherited mutation in one of these same genes. In these families, the "first hit" is inherited either in the egg or the sperm (this is known as a germline mutation). It affects all cells of the body. People who inherit a germline mutation in a cancer-associated gene are at increased risk of developing cancer. The pattern of cancer seen in such a family will depend on the specific gene involved and sometimes on the type and location of mutation in that gene.

There have been considerable advances in the area of cancer genetics over the last 15 years, with the identification and characterisation of genes in which germline mutations predispose to a high risk of cancer. These scientific advances in understanding the genetic predisposition have been translated into clinical practice as genetic testing for families with cancer predisposition has become available. This has been achieved by the development of familial cancer services throughout major centres in Australia, often within public-sector comprehensive cancer centres. Such services are staffed by clinical geneticists and/or oncologists with expertise in cancer genetics, supported by trained genetic counsellors and a molecular genetics laboratory. The role of the familial cancer service is to identify individuals at high genetic risk of cancer so that appropriate intervention strategies can be implemented for early detection or prevention, with the ultimate aim being to reduce the impact of cancer for the individual and their family.

Genetic predisposition to cancer

Family history has long been recognised as an important risk factor for cancer. The taking of a good family history is more important than ever.¹ National guidelines can assist health professionals to estimate the risk of cancer based on family history and to determine whether referral to a familial cancer service might be appropriate.^{2,3} In general, family histories of cancer that suggest genetic susceptibility include those with either three or more relatives on the same side of the family with the same (or related) cancer, or two affected individuals with the same (or related) cancer where there is an additional "high risk feature", such as earlier than average age at diagnosis or the presence of more than one primary cancer in a family member.

The role of the familial cancer service

A familial cancer service can be expected to construct a full three-generation pedigree on both sides of the family. Importantly, family history is often poorly reported and verification of the described family history is necessary. Gynaecological malignancy is commonly misreported and confirmation that the family account of ovarian cancer was actually a cervical intra-epithelial neoplasia, or that a reported breast cancer was simply a fibroadenoma, can dramatically change the assessment of familial risk. Verification of family history involves the genetic counsellor obtaining consent from family members to enable access to pathology reports and medical records.

At the clinic visit, an assessment of cancer risk may be made on the basis of family history, but this is generally a broad categorisation, placing an individual at "average risk", "moderate risk" or "potentially high risk", based on national guidelines. For those at potentially high-risk, due to a stronger family history, genetic testing (discussed below in further detail), can assist in further clarifying risk within some families. An offer of genetic testing can only be made if there are known genes in which heritable mutations cause an increased risk of cancer.

The well-known cancer susceptibility syndromes are reviewed in Nagy and Garber for general reference and further information is available through Australian websites.⁴⁻⁷ It should be recognised that genetic testing is now a mandatory part of the clinical management of Multiple Endocrine Neoplasia (Types 1 and 2), retinoblastoma, Familial Adenomatous Polyposis (FAP) and Von-Hippel Lindau syndrome, where the genes tested are MEN1, RET, Rb, APC and VHL, respectively. In these conditions there is a clear role for screening and prevention in reducing the impact of cancer for those at proven high-risk.^{6,7}

For families with a strong family history of breast and ovarian cancer, clinical testing usually involves the genes BRCA1 and BRCA2. Breast and thyroid malignancies with intestinal hamartomas (consistent with Cowden syndrome) may be investigated by testing the PTEN gene. A family history of bowel cancer, especially early onset (aged <50 years) and other cancers, including uterus, ovary, stomach, small bowel, renal pelvis or ureter, suggests the involvement of the mismatch repair genes in the syndrome of Hereditary Non-Polyposis Colon Cancer (HNPCC). Genetic testing for other polyposis syndromes, including Juvenile Polyposis and Peutz-Jeghers syndrome is now possible. On the other hand, genetic testing for familial melanoma is usually only available when a family CDKN2A mutation has already been identified as a result of participation in a research study. Furthermore, despite intensive research, no genes have yet been firmly identified in which mutations cause a hereditary tendency to prostate cancer. Finally, for some syndromes, such as the Li-Fraumeni syndrome, where there is a high risk of varied cancers (including paediatric sarcoma, haematological malignancy, early onset breast cancer, adrenal cancer, brain tumour and lung cancer), genetic testing for p53 may identify a causative mutation. However, for individuals with the Li-Fraumeni syndrome, there is currently little to offer in the way of proven screening or prevention, and so genetic testing needs to be considered with care.

Families with a significant family history of cancer can be enrolled in studies involved in genetic research. Australian research efforts, such as the Kathleen Cuninghame Consortium for Research on Familial Breast Cancer (kConFab), the Australian Breast Cancer Family Study (ABCFS) and Australasian Colorectal Cancer Family Study (ACCFS) will continue to make significant contributions to understanding the familial aspects of cancer.

Genetic testing for cancer susceptibility

In April 2003, the American Society of Clinical Oncology (ASCO) published an updated policy statement concerning genetic testing for cancer susceptibility: "ASCO recommends that genetic testing be offered when:

1) The individual has personal or family history features

suggestive of a genetic cancer susceptibility condition;

- 2) The test can be adequately interpreted; and
- 3) The results will aid in diagnosis or influence the medical or surgical management of the patient or family members at hereditary risk of cancer. ASCO recommends that genetic testing only be done in the setting of pre and post-test counselling, which should include discussion of possible risks and benefits of cancer early detection and prevention modalities."⁸

It is recommended that prior to consideration of cancer genetic testing, key components of the consultation should include medical and family history, cancer risk assessment and discussion of the limitations, as well as possible risks (eg. impact on future applications for life/disability insurance) and benefits of molecular genetic testing for the person and their family members. Informed consent must be obtained.⁹

Genetic testing is now available through familial cancer services for some of the common hereditary cancer syndromes listed above. Whatever the gene to be tested, the general principles remain the same. The first step in genetic testing is usually to take blood from one of the family members affected by the condition, although sometimes an unaffected obligate carrier may be tested instead. This must be done with fully-informed consent. Counselling before testing must cover the potential harms, benefits and limitations of such testing. The laboratory then searches the relevant gene(s) to determine whether a causative gene mutation can be found.

This first phase, the "mutation search", may take some months. A causative gene mutation cannot be found in every family, as mutations may be missed, or mutations may be present in other genes that are not yet identified. Importantly, this means that if the family history is strong and the genetic test (mutation search) fails to identify a gene mutation in an affected family member, that test result should be considered "inconclusive" and all relatives remain at potentially high-risk. However, if a causative mutation is identified in the relevant gene (eg. in BRCA1 or BRCA2 for a breast cancer family, or in a mismatch repair gene for an HNPCC family), then other at-risk family members (males and females) can be offered "predictive" genetic testing. Predictive tests are relatively cheap and quick, with results generally available in four to six weeks. Once the family gene mutation has been identified in the mutation search phase, others in the family can simply be tested for the presence or absence of that same gene fault.

The risk of cancer associated with the gene mutation and the approach to that risk requires discussion before testing. Those who are found not to carry the family mutation (at predictive testing), should be considered to be at average risk of cancer. They and their offspring can

be spared unnecessary cancer screening and concern.

Predictive genetic testing for cancer risk is usually restricted to adults unless there is a case for medical intervention in childhood, such as in families with Familial Adenomatous Polyposis, where screening starts in the teenage years. Pre-natal testing and pre-implantation genetic diagnosis is feasible once the family mutation is identified, but is not often considered in cancer families.

Conclusion

Genetic susceptibility to cancer is rare. It can generally be identified by taking a good family history. If genetic testing identifies a causative gene mutation, then predictive testing can identify those family members who do not carry the mutation and are "not at risk". It also identifies those who are "at high risk". The latter can take the opportunity to have intensive cancer screening including newer modalities, such as breast magnetic resonance imaging. They may wish to consider risk-reducing surgery, particularly in circumstances where this has a proven role.

Restorative procto-colectomy is the standard care for preventing bowel cancer in FAP, as the risk of cancer without such intervention is 100%. In carriers of a BRCA1 or BRCA2 gene mutation, risk-reducing salpingo-oophorectomy not only dramatically reduces the risk of ovarian cancer, but if done before menopause, halves the risk of breast cancer. Prophylactic mastectomy (with or without reconstruction) also significantly reduces

the risk of breast cancer. For children with an inherited RET gene mutation, prophylactic thyroidectomy prevents medullary thyroid cancer. In some cases chemoprevention can be used to reduce the risk of cancer. Tamoxifen may be considered as a risk-reducing option for high-risk women, although there are side-effects and evidence is not yet available regarding the impact of preventative tamoxifen on mortality from breast cancer.

Finally, for those at high genetic risk who do develop cancer, targeted therapies are being designed for tumours, depending on their molecular basis. As an example, BRCA1/2 deficient breast/ovarian cancers seem to rely on poly (ADP-ribose) polymerase (PARP) in response to DNA damage and specific inhibition. Using PARP inhibitors is now being studied in a Phase II trial of recurrent breast/ovarian cancers in BRCA1/2 carriers. Such developments will no doubt continue.

The improved ability to detect people at high-risk through analysis of their family history and genetic testing has been accompanied by advances in cancer screening, cancer surveillance and cancer prevention. It is important to identify these individuals so that these advances can be applied in their management, offering hope of making an impact on the national goals of cancer control.

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INFORMATION MANAGEMENT IN FAMILIAL CANCER

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Abstract

The diagnosis of a familial predisposition to develop cancer carries major implications for both the affected person and their well but worried relatives. But familial cancer can almost never be diagnosed on the basis of one person's experience; it is the shared cancer experience among relatives that enables the diagnosis to be made. Once this diagnosis has been made, it carries medical implications for the unaffected members of the family. Obtaining information about affected members of the extended family and sharing the collated information with unaffected relatives are major functions of familial cancer services. Managing this information flow raises a number of ethical, legal and practical issues, however Australia is fortunate in generally having a workable framework of legislation that permits this information flow. Managing information flow across a large family requires the resources of a familial cancer clinic,

When a patient is seen by a healthcare professional, it is usually a one-on-one relationship. There are, of course, social factors that may be crucial in the management of the case and relatives or friends may attend the

appointment. However, those factors revolve around the needs and capabilities of the patient in the room and the patient can readily provide consent for access to records and contact with other doctors.

Familial cancer is different. It is rarely possible to make a diagnosis of familial cancer solely on the basis of the patient's experience. The cancers that occur in most familial cancer syndromes are no different to the cancers found in other settings. For this reason, the key to the diagnosis of familial cancer is the pattern of cancer diagnoses seen among affected relatives. These relatives are usually not present in the clinic and may have died. This immediately raises the question as to how this information should be obtained, recorded and validated. Is the patient allowed to pass on information about these relatives? Can this information be recorded? Can this information be used when counselling another member of the family?

Once a diagnosis of familial cancer has been made using information about affected relatives, it carries significant implications for unaffected members of the family. They may be at increased risk of developing cancer and targeted prevention or surveillance programs may be warranted. These relatives are usually not clients of the clinic and may not even know of the family's history of cancer. Should at-risk relatives be advised of this medical information? Who should notify them? Would such a notification represent a breach of the privacy of the patient or of the relative being notified?

The management of familial cancer requires care in the collection of information from and dissemination of information to relatives. The legal and ethical framework for this information management is becoming clearer and it usually does not constitute a barrier to the effective care of the family as a whole. However, it is essential that all professionals involved in cancer care are aware of the benefits and potential risks of using family information.

Gathering information from relatives

It is accepted that the collection of private medical information about relatives is necessary for good clinical practice and that the information constitutes part of the medical history that the patient provides to the professional. In fact, it may be medico-legally negligent if a professional fails to solicit, document and correctly interpret this information. However, it has taken a long time to have this practice accepted under law. Under the Federal Privacy Act (1988), the collection of private information about potentially identifiable relatives was prohibited unless they provided consent. But obtaining such consent would be both unworkable and could represent a breach of the patient's privacy. After a successful appeal by ACHA Health (a private healthcare provider in South Australia) and the Human Genetics Society of Australia, a specific provision (Public Interest Determination 9A) was made in 2003, which allows healthcare providers to collect and record information about relatives from the patient without the relatives' consent, provided this information is relevant for the care of the patient.¹ (The federal legislation only applies to private sector organisations; most public sector health facilities fall under state privacy laws which, in general, reflect the federal law).

This provision is sufficient to record family information provided by the patient, including identifying information such as name and date of birth, to reduce the risk of errors and facilitate confirmation of reported diagnoses (see below). However, this provision does not allow the professional to release this information to another relative or health provider. At this point, the professional only has legal sanction to collect and use this information for the management of the patient's care.

It is not uncommon for reported diagnoses of cancer to be incorrect. This does not reflect a lack of care on the part of the patient; it is simply that medical information is not always reliably shared within families. Studies have shown that up to 20% of the reported cancer diagnoses in relatives are inaccurate.² The risk assessment provided by the professional to a patient is critically dependent on the accuracy of the reported family history and so it is necessary that cancer diagnoses be confirmed. In some states there is provision under State legislation for approved professionals to obtain details of cancer diagnoses directly from the State's Cancer Registry, without having consent from the relative. In other states this is not allowed and the relative must be contacted and asked to provide written consent.

A relative cannot be contacted directly by the professional regarding the release of this information, as such an intrusion is not sanctioned under the federal privacy legislation. Relatives need to be approached through the patient and asked to provide written consent for the professional to access the relative's medical records. The patient may indicate that they do not want to approach certain relatives and consequently the matter cannot be taken further. In the case of deceased relatives, which is a common issue, it is necessary to seek consent from the executor of the deceased relative's estate or from the next of kin. Such consent is sufficient to release medical information in most jurisdictions, but not in Queensland; in that state, the release of medical information about a deceased person is viewed under State law as a freedom of information request and is subject to the constraints of that legislation.

In our experience, 90% of the requests for access that are made are granted. It is rare for us to be advised that a request has been explicitly denied (<1% of requests) and we do not know why the remaining relatives do not provide consent. However, it is important to note that there is no right under federal law for a patient to gain access to a relative's records. In its exhaustive and highly commended review of genetics and privacy, the Australian Law Reform Commission proposed that a person be able to access appropriate elements of a close relative's medical record without consent if there was a clear medical benefit from doing so.³ However, the Federal Government rejected this proposal. This is an important point because, as detailed below, there is now provision under federal law for a healthcare professional to disclose information to relatives without consent. But there is no provision to obtain information from relatives without consent.

The process of obtaining this consent must be documented, with records of who was approached and retention of a hard copy of the signed consent form. This creates significant data management issues for busy clinical services. However, once consent has been

obtained, the professional can contact other healthcare providers such as hospitals, clinicians, pathology and laboratories to obtain the information pertinent to the primary purpose of the patient's consultation ie. assessment of the risk of familial cancer. It is not appropriate to obtain other information that does not relate to this primary purpose.

Disseminating information to relatives

Once a diagnosis of familial cancer has been made, and the appropriate risk minimisation strategy formulated, this is very significant information for the unaffected relatives, some of whom may still be children. This raises the issue of whether medical information should be provided to relatives, especially if they are not clients of the professional involved. This matter is usually discussed in the context of a familial mutation being identified in the family and of the process for notifying relatives that genetic testing is available to clarify their risk of cancer. However, the same principles apply to simply informing relatives that there is a risk of familial cancer, even if the causative mutation has not been found.

In the first instance, the professional must advise the patient that the diagnosis of familial cancer carries implications for relatives and they should seek medical advice. The fact that this advice has been given must be documented, as there is already clear evidence in case law that failure to provide such advice would be deemed negligent.⁴ Many clinical services also provide patients with multiple copies of a form letter, which provides the key information and contact details for the service, and recommend that these be distributed to relatives.

Leaving the notification of relatives in the hands of the patient has a number of advantages. It is cheap, the privacy of the family is assured and the patient can plan the best approach to a relative, including the possibility that the relative not be advised. However, this approach also raises problems. Firstly, it is not very effective. In our experience, only 20% of the eligible relatives actually seek information or genetic testing if risk notification is left in the hands of the patient. Secondly, many patients find the responsibility of informing relatives burdensome. This may be because they have significant issues of their own to address, such as their own illness, or because they do not have a good relationship with some relatives.

We have trialled writing to all eligible relatives, with the contact details being provided by the patient.⁵ In this way, the patient retains control over the communication to relatives, but is spared the responsibility for the communication. This process has resulted in a doubling of the proportion of eligible relatives seeking advice. The letter sent to relatives must be carefully worded to provide sufficient information, while not breaching the privacy of the patient. We do not chase up non-responders because each person has a right not to pursue further information. In the context of a familial cancer service, in which family information has already been collected to assist in making the diagnosis, the additional steps necessary to advise relatives in this way require few resources. However, this approach would be much more demanding in other clinical settings.

The success of this approach begs the question as to why it is not more successful. Why do 60% of eligible relatives who have been informed of the cancer risk and the availability of useful interventions, not seek further information to protect their own health? It is likely that there are issues of fear and complacency, but the short answer is that we do not know. We have found that men in families at risk of breast/ovarian cancer are less likely to respond, even though we do not specify the cancer risk in our letters.⁶ Clearly the 'bush radio' is working and these men are hearing about the specifics of the cancer risk from other family members. The 'bush radio' mechanism may also account for our observation that relatives living close to the patient are more likely to respond. These observations suggest that a combination of formal notification and informal encouragement may be the most effective strategy for spreading information. But we do not know why some people choose not to act on that information.

These processes for informing relatives are carried out with the patient's consent. But what if the patient declines to provide this information to relatives? To take an extreme but actual example: "I hate my brother and do not want to tell him anything that might save his life". This would be very confronting for any health professional and it is fortunate that such responses are rare. Sometimes the rationale is different, however the outcome is the same: "My brother would be too frightened by this information to have a colonoscopy, and so I won't tell him". Prevention is better than cure and genetic counsellors usually discuss the familial implications of a diagnosis or testing as part of the initial consultation. In effect, a genetic test is done on the family as a whole (albeit using one person's DNA) for the benefit of the family as a whole. Genes are not owned by an individual but are shared within a family, with relatives the patient may not even like.⁷ The familial implications of a test result are an explicit component of the formal consent process that must be completed prior to genetic testing. In practice, the patient is an autonomous individual and genetic testing could not be withheld on the basis that the patient would not share an important result with relatives. However, familial cancer clinics seek to address and resolve this issue before testing is initiated.

Nonetheless, there are situations in which a patient refuses to share medically significant information with at-risk relatives. In its report, the Australian Law Reform Commission recommended that the Federal Privacy Act be amended to allow health professionals to breach a patient's privacy and notify relatives without their consent in certain circumstances. The necessary amendment to the Privacy Act was passed late last year. The Human Genetics Advisory Committee of the National Health and Medical Research Council is developing guidelines for the implementation of this amendment and they will be ready in 2008. In brief, a health professional will be permitted to notify a relative of the patient of significant medical information if this is necessary to reduce the risk of serious medical harm to the relative. It is important to note that this privilege is permissive not mandatory ie. clinicians are not obliged to notify relatives. In addition, the privilege should

only be exercised when extensive attempts to obtain consent to notify have failed.

Conclusion

The genes that we share with our relatives are cords that bind us, for good and ill, to the medical fortunes of our extended families. Recognising the significance of these ties can pave the way for the effective management of a familial risk of cancer. The key to such an approach is information sharing - knowing what diseases the family as a whole has had and sharing this collated information with unaffected family members who have the most to gain from preventative and surveillance strategies. Most families are keen to share this information and Australia now has a framework for collecting and utilising this information effectively. It is now up to all healthcare professionals to play their part and to seek, document and use family history information in their daily practice.

MANAGEMENT OF WOMEN AT HIGH FAMILIAL RISK FOR BREAST AND OVARIAN CANCER

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Abstract

Women with a strong family history of breast and/or ovarian cancer have a greatly increased risk for the development of these diseases. The key question for these women is what they can do to ameliorate their cancer risk. Fortunately, there are now several interventions which clearly reduce breast and ovarian cancer risk in high-risk women. These include risk-reducing bilateral mastectomy and salpingo oophorectomy and chemoprevention with tamoxifen or raloxifene. For those women who do not undergo risk-reducing bilateral mastectomy, screening is generally recommended in order to try and detect breast cancers at an early stage. Breast magnetic resonance imaging has an emerging role in such screening programs. Cancer screening does not reduce cancer risk and its impact on reduction of mortality in this group is uncertain. Women at high risk should be fully informed of their surgical, chemopreventive and screening options. A risk management plan should be tailored to each woman, particularly taking into account the level of her short-term (rather than life-time) risk, her lifestyle plans (such as child-bearing), competing risks (particularly in women with a prior cancer) and her personal preferences. The risk management plan should be reviewed regularly

Who is at high risk for breast/ovarian cancer?

Breast cancer and ovarian cancer are diagnosed in about 12,000 and 1100 Australian women per year respectively.¹ Between 1% and 5% of all breast cancer cases and around 10% of invasive epithelial ovarian cancer cases are due to the inheritance of mutations in known cancer predisposition genes.^{2,3}

In less than 1% of the population, the number of blood relatives affected with cancer, their ages at diagnosis and the types of cancers suggest a high likelihood of a dominantly-inherited mutation in a breast cancer and/or

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ovarian cancer-predisposition gene (see Table 1).

Referral of such women to a family cancer centre for formal risk assessment, consideration of genetic testing and discussion of management options is considered by many to be a standard of care.

BRCA1 and BRCA2 are the genes most commonly associated with breast and ovarian cancer predisposition. Carriers of mutations in these genes have a significantly elevated lifetime risk of breast cancer or ovarian cancer.^{4,5} Several other genes are also associated with an increased risk of breast and/or ovarian malignancy

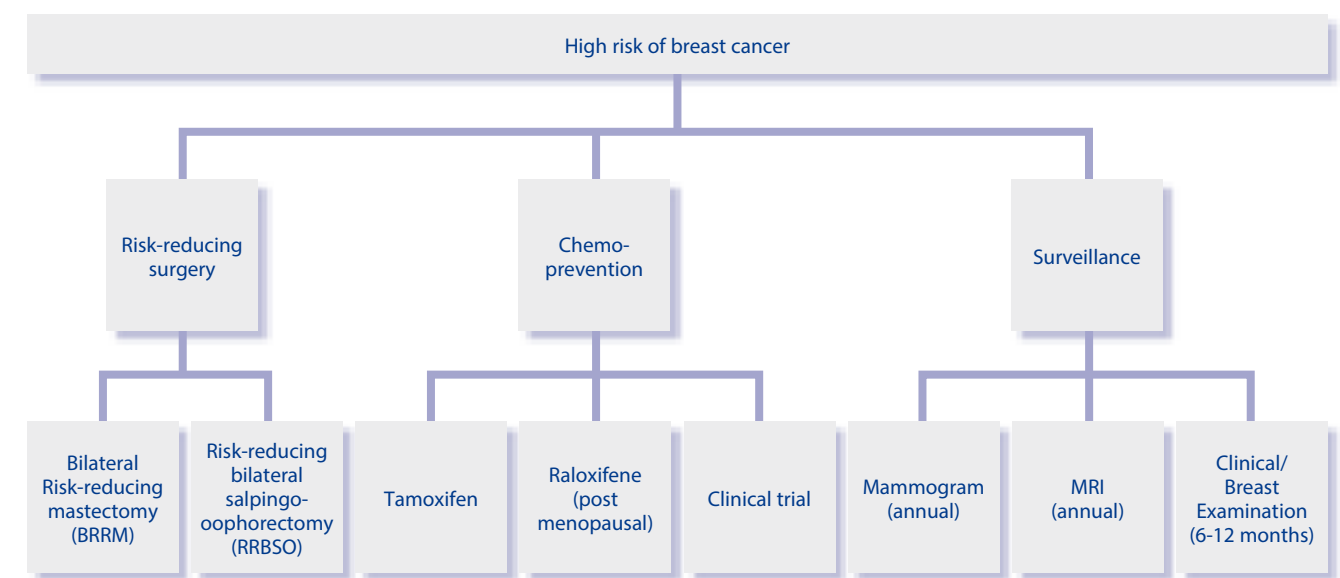
Table 1: Risk of breast or ovarian cancer based on family history alone^{113,114}

Cancer type	Features	Lifetime risk	% of population
Breast cancer	Two 1st or 2nd degree relatives (same side of family) with breast or ovarian cancer. plus one or more of: n additional relative(s) with breast or ovarian cancer n onset of breast cancer before the age of 40 n bilateral breast cancer n breast and ovarian cancer in the same woman n Ashkenazi Jewish ancestry n breast cancer in a male relative or One 1st or 2nd degree relative diagnosed with breast cancer ≤45yo, plus another 1st or 2nd degree relative (same side of family) with sarcoma (bone or soft tissue) ≤45yo	25-50***%	<1%
Ovarian cancer	One 1st degree relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry. Two 1st or 2nd degree relatives (same side of the family) diagnosed with ovarian cancer, especially if ≥1 of the following: n additional relative(s) with breast or ovarian cancer n onset of breast cancer before the age of 40 n bilateral breast cancer n breast and ovarian cancer in the same woman n breast cancer in a male relative Three or more 1st or 2nd degree relatives on the same side of the family diagnosed with any cancers associated with HNPCC*: n colorectal cancer (especially if <50y) n endometrial cancer	3-30%**	<1%

Table 2: High risk genes, frequency and increased risks of breast and ovarian cancer^{115,116}

Gene	Syndrome	Breast cancer risk by age 70yo	Ovarian cancer risk by age 70yo	Associated cancers
BRCA1	Hereditary breast/ovarian cancer	39-87%	20-40%	Pancreas
BRCA2	Hereditary breast/ovarian cancer	26-91%	10-20%	Prostate Pancreas
p53	Li-Fraumeni Syndrome	>90%	n/a	Soft tissue sarcoma Osteosarcoma Brain tumours Adrenocortical carcinoma Leukaemia Colon
PTEN	Cowden Syndrome	25-50%	~1%	Thyroid Endometrial Genitourinary
STK11/LKB1	Peutz-Jeghers Syndrome	45-54%	(usually sex cord tumors rather than epithelial ovarian cancer)	Small intestine Colorectal Uterine Testicular
CDH1	Hereditary diffuse gastric carcinoma	39% (lobular)	n/a	Diffuse gastric cancer
MLH1, MSH2, MSH6, PMS1, PMS2 (mismatch repair)	Hereditary non-polyposis colorectal cancer/ Lynch syndrome	n/a	10%	Small intestine Colorectal Stomach Uterus Ureter/renal pelvis

Figure 1. Breast cancer: risk reduction and surveillance strategies



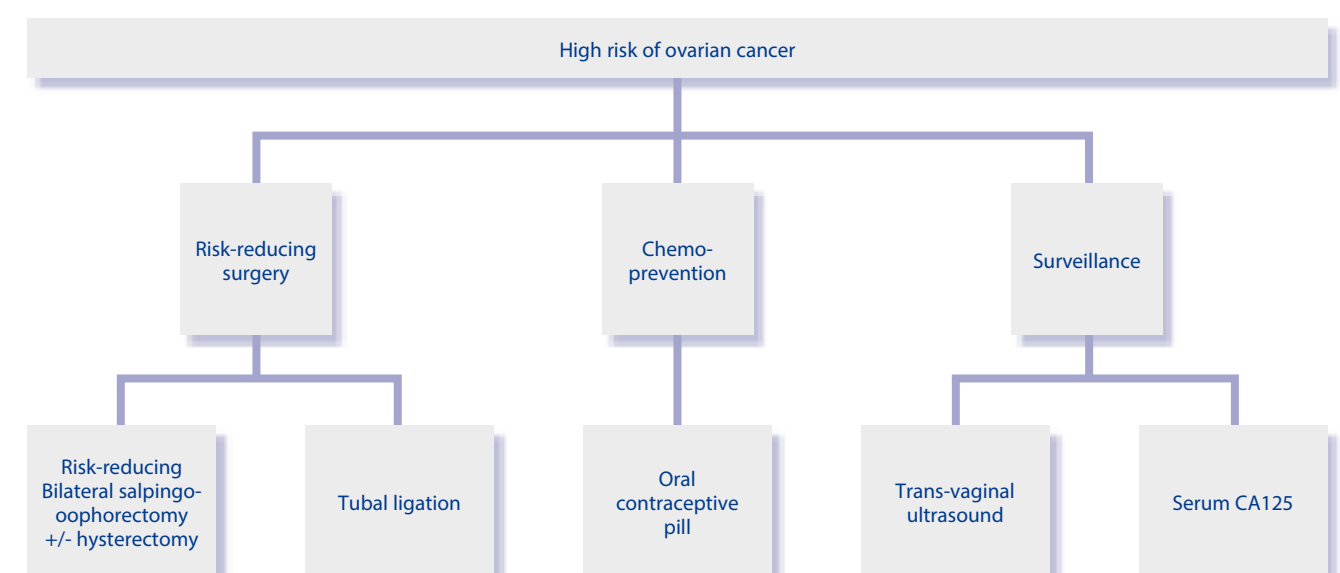
(see Table 2).

Families meeting high risk criteria (see Table 1), but in whom a mutation cannot be found, are still considered at high risk because genetic testing is not 100% sensitive, and because there may be a mutation in an as yet unidentified cancer predisposition gene.

What are the risk management options for high-risk women?

Management of women with a strong family history and/or a documented gene mutation is complex and dynamic. Optimal risk management is likely to be in the context of a multidisciplinary team. Multidisciplinary risk management clinics have been set up at several family cancer centres within Australia.⁶ Figures 1 and 2 outline the options with respect to risk management strategies currently available.

Figure 2. Ovarian cancer: risk reduction and surveillance strategies



Risk-reducing surgery

An individual's level of risk should be fully clarified prior to undertaking risk-reducing surgery. If possible, genetic testing of a family member with cancer should occur. If a mutation is found, the woman contemplating surgery should be tested for that mutation. In that way, unnecessary surgery in women who have not inherited the cancer causing family mutation can be avoided.

Bilateral risk-reducing mastectomy

Bilateral risk-reducing mastectomy (BRRM) is the most effective method of breast cancer prevention, reducing risk by about 90%.⁷⁻¹⁰ It is usually done in conjunction with immediate reconstruction. Total mastectomy is likely to reduce risk more than subcutaneous mastectomy, however the latter is a reasonable option for women wishing to retain the native nipple and areola complex,¹¹ provided they are informed that the benefits may be slightly less. BRRM carries the risk of surgical complications;¹² additionally cosmetic complications following reconstruction may occur.¹³

In descriptive studies women who have undergone BRRM report lessened concern about cancer and decreased perceived cancer risk,¹⁴⁻¹⁶ but also dissatisfaction with reconstruction,¹⁷ feelings of femininity and sexual relationships.^{14,18} Because BRRM can have adverse psychological and body image consequences, it should not be performed without prior counselling.

In Australia, uptake rates for BRRM have been relatively low by international standards.¹⁹ In high-risk women attending family cancer clinics, (90% of whom were not known mutation carriers), the uptake rate over a three-year follow-up period was 4.4%. Those who underwent the procedure were more likely to have more first degree relatives with breast cancer than those who did not.¹⁶ In another study of mutation carriers in the kConFab research cohort,²⁰ the uptake rate of BRRM was 11%, three years after learning their mutation result.²¹

Risk-reducing bilateral salpingo-oophorectomy

Risk-reducing bilateral salpingo-oophorectomy (RRBSO) reduces ovarian and fallopian tube cancer risk by about 90% and, for premenopausal women, also reduces breast cancer risk by about 50% in BRCA1 and BRCA2 mutation carriers.²²⁻²⁷ RRBSO has recently been shown to reduce overall and cancer specific mortality.²² It is an appropriate option for women who carry a BRCA1 or BRCA2 mutation, or who have a family history of breast and epithelial ovarian cancer (but is not generally recommended for women with a breast cancer-only family history). In Australia, uptake rates for RRBSO have been higher than for BRRM, with approximately 30% of mutation carriers undergoing RRBSO within three years of learning of their mutation result.²¹

RRBSO includes removal of the fallopian tube because of the increased risk of fallopian tube cancer in these women. Concurrent hysterectomy increases the

complexity of the surgery, but is sometimes advocated to avoid the risk of endometrial cancer if progesterone-containing HRT or tamoxifen is planned for subsequent use. Primary peritoneal carcinoma may occur despite RRBSO,²⁸ with the rates of such malignancies varying from 2-11%.²⁹

For pre-menopausal women, RRBSO causes abrupt menopause. Observational studies suggest that the use of hormone replacement therapy (HRT), after RRBSO in BRCA1/2 mutation carriers, does not offset the breast cancer risk reduction conferred by the procedure.³⁰ Results from the US based Women's Health Initiative Study suggest caution in advising prolonged post-menopausal HRT in women.^{31,32}

Optimal timing of RRBSO is controversial and needs to be individualised. Clearly it should not be undertaken until childbearing is completed. Ovarian cancer risk does not generally start to increase above that of the general population until about age 40 (BRCA1 carriers) or 50 (BRCA2 carriers). Thus, if ovarian cancer risk reduction is the major objective (eg. the patient is using other strategies to decrease breast cancer risk), surgery can be delayed until age 35-40 in BRCA1 carriers and age 45-50 in BRCA2 carriers. However, if reduction in breast cancer risk is also an objective, earlier RRBSO may be appropriate.

Tubal ligation

Tubal ligation has been associated with decreased risk for ovarian cancer in observational studies.³³⁻³⁵ One case control study showed that tubal ligation reduced ovarian cancer risk by about 60% in BRCA1 carriers. A protective effect was not seen in BRCA2 carriers, however was not excluded.³⁶ In BRCA1/2 mutation carriers who have completed childbearing, but who choose not to undergo premenopausal RRBSO, tubal ligation should be considered as an effective contraceptive means which may also decrease ovarian cancer risk.

Chemoprevention

Breast cancer chemoprevention

Chemoprevention, with the selective oestrogen receptor modulators (SERMs) tamoxifen or raloxifene, reduces breast cancer risk by about 40%.³⁷⁻⁴² Tamoxifen is the only evidence-based option for pre-menopausal women; for post-menopausal women raloxifene is also an option. These two agents have been compared in a randomised trial and are equally efficacious in preventing oestrogen receptor positive invasive breast cancers, with tamoxifen superior for prevention of non-invasive cancers.⁴³ Raloxifene is associated with fewer gynaecological side-effects, thromboembolic events and cataracts than tamoxifen. These agents probably should not be used in women with previous history of deep venous thrombosis, smokers, or those with other uncontrolled cardiovascular risk factors.

SERMs have not been shown to reduce risk for

oestrogen receptor negative breast cancer and this has been used as an argument against using them in BRCA1 carriers, who usually develop ER negative tumours.^{44,45} Indeed, a sub-analysis of mutation carriers in the largest prevention trial suggested that the benefit of tamoxifen might be limited to BRCA2 carriers, however the study was under-powered and included fewer than 10 BRCA1 carriers.⁴⁶ Although BRCA1 associated breast cancers are usually oestrogen receptor negative, initiation of these tumours may well involve the oestrogen pathway,^{47,48} which is consistent with the observation that interventions reducing oestrogen exposure in these women (eg. pre-menopausal oophorectomy), appear to reduce risk. For this reason, tamoxifen chemoprevention may be considered a reasonable option, although enrolment in trials of novel chemoprevention agents such as retinoids should be considered.⁴⁹

Aromatase inhibitors show promise as chemopreventive agents, based on their ability to reduce contralateral breast cancer risk in the adjuvant disease setting.⁵⁰ A clinical trial of anastrozole as chemoprevention (IBIS II) is underway. Participation should be discussed with high risk women, particularly those with a contraindication to SERMs.

Ovarian cancer chemoprevention

While there are no randomised trials, observational studies demonstrate a reduced risk of ovarian cancer in the general population and in high risk individuals who take the oral contraceptive pill.^{33,51-54} Most studies suggest up to a 50% reduction in the risk of ovarian cancer in BRCA1/2 carriers.^{53,55,56} Oral contraceptive pill use in this setting has been tempered by concern about the effect on breast cancer risk (discussed below in the 'lifestyle factors' section). However, as ovarian cancer carries a higher mortality rate than breast cancer, in premenopausal women who choose not to undergo RRBSO, the oral contraceptive pill is a reasonable strategy to reduce risk, while being mindful of the uncertainty regarding impact on breast cancer risk. For women who have undergone BRRM, but wish to postpone RRBSO until later, it is potentially a useful strategy as there is no concern about the possible impact on breast cancer risk.

Surveillance strategies

Surveillance strategies do not reduce cancer risk, however are aimed at detecting malignancy at an early stage when it may be amenable to curative treatment. Evidence on the efficacy of intensive surveillance in high risk women is limited.

Breast cancer screening/surveillance

Mammography

In the general population, mammographic screening has been demonstrated to reduce breast cancer mortality in women older than 50 years by 20-25%.^{57,58} The efficacy of mammographic screening in younger, high

risk women remains controversial.⁵⁹ Anecdotal reports document both success and failure of mammography to detect breast cancer in carriers of BRCA1 mutations,⁶⁰ and the sensitivity of mammographic screening in high-risk women over a variety of studies ranges from 50-91%.⁶¹

Some have suggested that annual mammography may not be frequent enough in BRCA1 mutation carriers because these cancers are usually high grade and may develop between screens.⁶²⁻⁶⁴ However, enthusiasm for more frequent mammographic screening is limited, partly by the question of whether ionising radiation may induce cancers in mutation carriers, because these individuals may have difficulty repairing DNA damage caused by radiation.⁶⁵ Studies have had conflicting results. Two studies of BRCA1/2 carriers found no increased risk of breast cancer associated with mammography.^{66,67} However, a recent retrospective cohort study of 1601 BRCA1/2 carriers demonstrated an increased risk of breast cancer (HR1.54, p=0.007) with any reported exposure to chest x-rays, especially in younger women.⁶⁸

Currently, women at high risk are recommended to undergo annual mammography, either from the age of 40 or five years earlier than the age at diagnosis of the youngest breast cancer case in the family, whichever is earlier. For women with proven gene mutations mammographic screening is often considered in the 30s.

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is an emerging screening modality for high risk women because of its high sensitivity.^{69-75,76} The American Cancer Society supports annual MRI screening for individuals with a known BRCA mutation, individuals untested but with a first-degree relative with a BRCA mutation and individuals with an estimated lifetime breast cancer risk >20-25%.⁷⁶ The European National Institute for Health and Clinical Excellence (NICE) guidelines recommend annual MRI in similar circumstances and in those with TP53 mutations a 10-year risk of >8% (30-39yo), or a 10-year risk >12% with dense breasts on mammography (40-49yo).⁷⁷

The high sensitivity of MRI screening is offset to some extent by its low specificity. This results in high false-positive rates, which may result in anxiety and unnecessary biopsy. There is no data on mortality benefits and lead-time bias may be a factor. While further research is needed, many Australian clinicians have begun to adopt the practice of MRI surveillance in high-risk women.

Breast clinical and self-examination

Clinical breast examination (CBE) may be an important adjunct in breast cancer screening in young, high risk women, as it may detect mammographically silent cancers, or may detect interval cancers between mammographic screenings. In addition, CBE is a

potentially useful modality when women are pregnant or breast-feeding and other screening modalities are contra-indicated. It is generally recommended that CBE be carried out every six to 12 months in high risk women. While there is no evidence of survival benefits from breast self-examinations, women should be encouraged to be aware of how their breasts look and feel, and report any changes promptly.

Ovarian cancer screening/surveillance

Despite mounting evidence from observational studies that it is of no benefit, ovarian screening is sometimes considered for high risk women who have not undergone RRBSO.⁷⁸ Screening tests usually consist of transvaginal ultrasonography with serum CA125 levels.⁷⁸⁻⁸¹ Women who choose ovarian screening rather than RRBSO should be fully informed of the lack of evidence for any benefit.

Lifestyle factors

Lifestyle and environmental factors may modify breast cancer risk, although the effects are modest compared with surgery or chemoprevention. Current evidence is limited for several reasons. Most studies of modifiers of cancer risk in high risk women have been retrospective, prevalent case control designs, which have a high likelihood of systematic biases, including recall and survivorship bias. The few prospective studies are small or cobbled together from multiple institutions, using non-systematic and non-uniform follow-up strategies. Non-random loss to follow-up is a major potential source of bias in these studies. Additionally, most studies have focused on mutation carriers rather than the much larger population of women who have a strong family history but lack an identified gene mutation.

Parity

Increasing parity and early age at first childbirth are protective in the general population against breast cancer development. While several studies have investigated the effect of parity and age at first birth on breast cancer risk in BRCA1 and BRCA2 mutation carriers, results have been inconsistent.⁸²⁻⁸⁷ However, the advantage of early childbearing for mutation carriers is that it allows earlier use of other effective risk management strategies such as risk reducing surgery and chemoprevention.

Breastfeeding

In the general population, a woman's breast cancer risk reduces by about 4% for every 12 months of breastfeeding.⁸⁸ Several studies of mutation carriers have shown a reduction in breast cancer risk associated with breastfeeding.^{85,86,89} The single study which did not show any risk reduction was inadequately powered to exclude benefit.⁸⁴ Women who are at high risk should breastfeed for as long as practical and preferably beyond one year.

Oral contraceptive use

Use of the combined oral contraceptive pill reduces ovarian cancer risk in the general population and in BRCA1 and BRCA2 mutation carriers. Whether oral contraceptive pill use affects breast cancer in high risk individuals remains controversial. A meta-analysis of 54 studies showed that current oral contraceptive pill use is associated with a 24% increase in breast cancer risk, but the risks were similar for those with and without a family history of breast cancer.⁹⁰ Two other studies have not demonstrated a significant effect of oral contraceptive pill use on breast cancer risk in women with a family history.^{91,92} Conversely, one study showed a three-fold increase in breast cancer risk among women who used the oral contraceptive pill and had a first degree relative with breast cancer.⁹³

In BRCA mutation carriers, two studies have shown no increase in risk in BRCA1 carriers who used oral contraceptive pills for at least one year,^{94,95} and one showed an increased risk of about 20% in ever-users of oral contraceptive pill.⁹⁶ Of these three studies, two showed no effect of oral contraceptive pills on breast cancer risk in BRCA2 mutations, however one showed an increased risk for BRCA2 carriers after at least five years of use. Thus, at this stage, there is no consistent evidence to suggest that the oral contraceptive pill is either safe or contra-indicated in women at high risk for breast cancer.

Obesity

There is clear evidence in the general population that obesity is associated with significantly increased breast cancer risk.^{97,98} Data on the effect of weight control on breast cancer risk in mutation carriers is very limited, however the published data does suggest that this may be an important area of risk management.^{99,100}

Alcohol consumption

Alcohol is clearly associated with breast cancer risk in the general population, with risk increasing by about 9% per daily standard drink.¹⁰¹⁻¹⁰⁴ Few studies have addressed the influence of alcohol in high risk women. One study found a 2.4-fold increase in breast cancer risk in daily drinkers with a strong family history of breast cancer.¹⁰⁵ Conversely, the only published study in mutation carriers showed no increased risk of breast cancer associated with alcohol consumption in carriers aged less than 50.¹⁰⁶ Given the other adverse health effects of excessive alcohol, it may be prudent to recommend that high risk women drink no more than one standard drink per day.

What about risk management in high-risk women with cancer?

Women with a personal diagnosis of breast cancer may be identified as belonging to a high risk family. Risk management for such women should consider the risk for a subsequent breast cancer or ovarian cancer and the competing risk of dying from their prior cancer,

which attenuates the prevention benefits. Referral to a family cancer centre for urgent genetic testing may be appropriate in planning both loco-regional and systemic management. For women who carry a mutation in BRCA1 or BRCA2, the risk of a second breast cancer is around 40%^{107,108} and ovarian cancer risk is also increased.¹⁰⁹

The most effective preventative strategy against development of a new breast cancer in BRCA1/2 positive individuals with a prior history of breast cancer, is complete mastectomy (if the previous operation on the affected breast was less than a mastectomy) with contralateral mastectomy, which reduces the risk of contralateral breast cancer by 90%.¹¹⁰ In mutation carriers with a low risk of systemic recurrence of their prior breast cancer, this operation should be considered prior to adjuvant breast irradiation, as the latter can limit the reconstructive options. Similarly, RRSO should be considered if the prognosis from the breast cancer is reasonably good; additionally, the subsequent oestrogen deprivation may be an effective adjuvant therapy in pre-menopausal hormone receptor positive women.¹¹¹ Conversely, in women who are at high risk for systemic recurrence, it may be pertinent to wait two to five years before proceeding with risk reducing surgery, which will be of no benefit if her previous cancer recurs systemically. However, these decisions are complex and should involve the input of experts in breast cancer genetics, the treating oncologist and the woman herself.

If risk reducing mastectomy is not performed, secondary chemoprevention may be considered. Tamoxifen appears to reduce contralateral breast cancer risk by about 50% in mutation carriers, including BRCA1 carriers (who usually do not receive adjuvant tamoxifen for treatment of their hormone receptor negative breast cancers).¹¹²

Management of subsequent breast cancer risk in women with prior ovarian cancer will be highly influenced by the stage and prognosis of the ovarian cancer. For women with advanced ovarian cancer, where the five-year survival rates are low (even taking into account the possible better survival from ovarian cancer in BRCA mutation carriers), management of breast cancer risk with screening and/or chemoprevention may be preferable to BRRM, whereas BRRM may be appropriate for women with early stage ovarian cancer.

Conclusion

The management of women at high risk of breast and ovarian cancer is complex and requires individualisation based on a woman's age, childbearing potential, personal risk and wishes. The great promise of predictive genetic testing for cancer predisposition in improving public health will only be realised with widespread implementation of evidence-based risk reduction strategies by the oncology and genetics community.

Acknowledgement

We would like to thank Dr Prue Francis for her critical review of the section of this article pertaining to management of high risk women with prior cancer.

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MANAGEMENT OF HIGH GENETIC RISK OF BOWEL CANCER

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Abstract

The identification and appropriate genetic counselling of individuals at high genetic risk of bowel cancer is an excellent example of how improved understanding of the genetic basis of disease can lead to a reduction in morbidity and mortality. The key to good management is to make as accurate a diagnosis of the family syndrome as possible, since different syndromes require different surveillance regimens. Diagnosis requires not only verification of cancer diagnoses in the family, but also consideration of the number and types of polyps detected at colonoscopy and in colectomy specimens. In addition, assays to detect microsatellite instability in cancer specimens aid in the diagnosis of Lynch syndrome. Since

Bowel cancer offers an opportunity for prevention available for virtually no other solid tumours. Not only can mortality be reduced by early detection of cancer, but in many cases the very occurrence of cancer can be greatly reduced without major surgery. This is because the disease develops in pre-malignant polyps which can be removed during surveillance colonoscopy, upper endoscopy and enteroscopy. Even in cases where the polyps are too numerous to safely control endoscopically,

they can be identified in the pre-malignant phase and appropriate surgery planned electively.

However, endoscopic procedures are relatively invasive and carry some risk of morbidity and mortality. To use them appropriately in individuals at high genetic risk requires understanding of the natural history of the various genetic syndromes. Most polyps are adenomas and occur predominantly in the colon and rectum. They

generally take between five and 15 years to evolve into invasive cancer. Thus for individuals with a moderately increased risk of bowel cancer, without the features of the specific genetic syndromes discussed below, colonoscopy every five years is appropriate to interrupt the natural history and greatly reduce the risk of cancer. If polyps are identified, increased frequency of colonoscopy may be appropriate according to published guidelines.¹

For all the specific inherited susceptibility syndromes discussed below, the natural history of the polyps differs significantly from the above. Thus, the first and most important step in recommending appropriate surveillance is to make the most accurate diagnosis possible, based on the verified clinical history of as many family members as possible and including consideration not only of cancers but also the numbers, location and histological characteristics of polyps. As discussed by Kirk (in this issue of Cancer Forum), this may be confirmed by finding a causative germline mutation in an affected family member. But if the family has convincing clinical features of a genetic syndrome, a negative mutation search in a definitely affected family member should be regarded as “inconclusive” rather than negative; the family should be managed according to the clinical diagnosis, with periodic attempts to clarify the mutation status as technology and knowledge advances.

Familial Adenomatous Polyposis (FAP)

In classical FAP, individuals develop over 100 and often thousands of adenomatous polyps in the second and third decade of life.² Although each individual polyp is no more likely than any other adenoma to progress to cancer, the sheer numbers of adenomas and the early onset mean that colorectal cancer is virtually inevitable, with an average age of onset of 39 years. Adenomas also occur in the duodenum and periampullary adenocarcinoma is the most common threat to life in patients who have undergone colectomy.³ Patients are also at risk of other extracolonic tumours, including intra-abdominal fibromatosis (desmoid tumours), papillary carcinoma of the thyroid and hepatoblastoma, however the lifetime risk of these is relatively low and there is no evidence to support screening.

FAP is due to mutation in the APC tumour suppressor gene and is inherited as an autosomal dominant trait with very high penetrance. About 30% of cases are due to de novo mutations.⁴ Mutation searching is successful in over 85% of families. There is some genotype-phenotype correlation in classical FAP, however there is heterogeneity in clinical course, even between family members with the same mutation. Thus identification of the exact mutation is of limited value in planning management.

The recommended surveillance protocol for at-risk individuals is flexible sigmoidoscopy, annually or biennially, from age 12-15 years to at least age 30-35 years.⁵ Once polyps are identified, prophylactic colectomy is planned. Appropriate surgical options are either total colectomy and ileorectal anastomosis, or restorative proctocolectomy

with pouch formation. Lifetime surveillance of the rectum or pouch is needed because of the ongoing risk of cancer. If the causative mutation has been identified in the family, predictive testing is usually offered at the age at which flexible sigmoidoscopy screening would commence. Mutation positive individuals should then undergo annual sigmoidoscopy. Surgery is not planned until there is pathological confirmation of the development of adenomas. Regular upper endoscopy to identify duodenal adenomas is advised after age 25.⁵ Management of duodenal polyposis is very challenging as it is technically difficult to remove the polyps endoscopically and duodenectomy may be associated with high morbidity and mortality. Management of such patients should be in a tertiary centre.

It is now recognised that certain APC mutations result in an attenuated phenotype where individuals develop less than 100 adenomas, onset is at a later age and adenomas tend to be flat and may only be present in the proximal colon.² The lifetime risk of colorectal cancer is very high. Surveillance needs to be with colonoscopy, rather than flexible sigmoidoscopy, since significant adenomas may be present in the proximal colon when none have developed distally. Because of the later age of onset, surveillance does not usually need to commence until age 18. In some cases prophylactic surgery can be avoided, if polyp numbers remain low enough for the colonoscopist to be confident that all adenomas can be removed at each colonoscopy, but this decision needs to be individualised. Patients are also at risk of duodenal adenomas.

MYH-associated polyposis

The phenotype of this autosomal recessive condition mimics attenuated FAP. This is not surprising, since the molecular defect is biallelic, inactivating germline mutations in the base excision repair gene MYH, which normally produces a protein which repairs G to T (guanine to thymine) transversions in the APC gene.² Thus individuals with this genetic defect frequently inactivate APC in colonocytes and develop large numbers of adenomas at a young age. Affected or at-risk individuals need to be managed as described above for attenuated FAP. Generally, genetic testing is only offered for the common mutations, however more extensive mutation searching is worthwhile, especially in individuals with a typical clinical picture and who are heterozygous for a common mutation.

Hereditary Non-polyposis Colorectal Cancer/ Lynch Syndrome

The natural history of colorectal carcinogenesis is fundamentally different in hereditary non-polyposis colorectal cancer (HNPCC) as compared to that described above in moderate risk families, FAP and MYH-associated polyposis.⁶ Despite its name, cancer does develop in polyps in this syndrome, but rather than there being a vast excess of adenomas, individual adenomas in individuals with HNPCC have a much

Figure 1: Guidelines for patients whose cancers should be tested for MSI to identify possible hereditary non-polyposis colorectal cancer (Lynch Syndrome)

Bethesda Guidelines

1. Colorectal cancer under 50 years.
2. Synchronous or metachronous colorectal cancer or other HNPCC-associated cancer regardless of age.
3. Colorectal cancer with MSI-H histology under age 60.
4. Colorectal cancer with one first degree relative with colorectal cancer or other HNPCC-associated cancer with one of the cancers being diagnosed under 50 years.
5. Colorectal cancer with two or more first or second degree relatives with colorectal cancer or other HNPCC-associated cancers regardless of age.

greater risk of rapidly developing into invasive cancer. The estimated risk of colorectal cancer in affected individuals is approximately 70% by age 70 years. About two-thirds of cancers are in the proximal colon, unlike sporadic colorectal cancers which are more common distally.⁷ Development of multiple primary cancers is common. The estimated lifetime risk for affected women developing endometrial cancer is 40-60%.⁷ There is also an increased risk of cancers of the small intestine, ovary, hepatobiliary system, kidney and ureter.

HNPCC is an autosomal dominant condition due to germline mutation in one of the family of DNA mismatch repair genes. Most families have mutations in MLH1 or MSH2, but a significant minority have mutations in MSH6 or PMS2. Unlike FAP, de novo mutations are very rare and there is nearly always a family history of the disease, if the family history is truly known. Mutation of MSH6 is associated with a somewhat lower risk of colorectal cancer with a later age of onset, however the risks of endometrial cancer are at least as high as for the other genetic defects.⁷ Dysfunction of the mismatch repair system leads to defective repair of mutations occurring during normal cell division. Thus in susceptible tissues, such as colonic polyps, somatic mutations occur in important cancer-related genes and cancer rapidly develops.

In cancers that develop due to defective DNA mismatch repair, repetitive DNA sequences, known as microsatellites, are especially prone to accumulate mutations and microsatellite instability (MSI) can be assayed in cancer tissue as a biomarker of HNPCC. Interpretation of MSI results needs to include an understanding that 10% of sporadic colorectal cancers exhibit MSI due to somatic inactivation of MLH1. Interestingly, both HNPCC and sporadic colorectal cancers which display a high level of MSI, have distinctive histological features including mucinous histology, poor differentiation and tumour infiltrating lymphocytes.⁸ Deficiency in mismatch repair in cancer tissue can also be assayed by performing immunohistochemistry for MLH1, MSH2, MSH6 and PMS2 proteins. Absence of one of these proteins indicates mismatch repair deficiency. Since these proteins act as heterodimers and loss of one partner destabilises the other protein, loss of MLH1 is accompanied by secondary loss of PMS2 and loss of MSH2 by secondary loss of MSH6. The results of MSI testing correlate very closely with

immunohistochemistry, although occasionally a protein may be detectable on staining despite being dysfunctional.⁹

The ability to test cancer tissue for MSI is very useful in diagnosing HNPCC, since the phenotype of an individual patient is much less distinctive than in any of the polyposis syndromes. Before the genetic defect was understood the Amsterdam criteria, which specify a very strong family history of colorectal cancer with early age of onset and autosomal dominant inheritance, were used as a diagnostic tool.⁷ However, many HNPCC families do not meet these criteria, especially if the family size is small and some families with other, as yet not understood genetic predispositions, do meet them. It is now recommended that MSI and/or immunohistochemistry be performed on the cancers of a much broader range of individuals who have some indication of possible HNPCC.^{5,7,10,11} These criteria have been formalised into the Bethesda criteria as outlined in Figure 1.¹¹

In 2006, the Royal College of Pathologists of Australasia issued a position statement recommending there be no requirement for additional consent or genetic counselling prior to performing MSI or immunohistochemistry for mismatch repair proteins. If this testing indicates HNPCC is likely in an individual meeting the Bethesda criteria, they should then be offered genetic counselling and further investigation to confirm the diagnosis, as outlined by Kirk in this issue of Cancer Forum, for other high risk families. If a family is referred directly to a genetic service with a history suggestive of HNPCC, archival cancer material on affected family members will be retrospectively tested to help confirm the diagnosis before a mutation search is undertaken. Immunohistochemistry is especially helpful in this regard since it indicates which gene is likely to be mutated.

Once a family has been diagnosed as transmitting HNPCC, all affected individuals and those at risk of the disease should be offered surveillance. If the germline mutation has been identified, those at risk can be offered predictive testing so that only those carrying the mutation need continue with surveillance. Surveillance should be by colonoscopy to the caecum annually or at least once every two years, beginning at age 25 or five years younger than the youngest affected family member (whichever is the earliest).^{5,7} This frequent screening is essential to prevent interval cancers which would otherwise occur due to the different mechanism of carcinogenesis in HNPCC.

Individuals with HNPCC often develop cancer in very small, recently formed adenomas. There is no evidence that CT colography ("virtual colonoscopy") is a safe alternative and it is known to have poor sensitivity for small polyps. The efficacy of screening for extracolonic cancers has not been demonstrated, however it is generally recommended that patients be offered the following tests annually:

- n transvaginal ultrasound from age 30 to 35 with endometrial sampling if there is endometrial thickening;
- n CA-125 measurement (after the menopause);
- n consideration of upper endoscopy in families where upper GI tract cancers have occurred.

If an individual with HNPCC presents with colorectal cancer, consideration should be given to total colectomy and ileorectal anastomosis because of the high risk of metachronous cancer. In addition, if the patient is female and past childbearing years, prophylactic hysterectomy and oophorectomy should be discussed. However, these decisions need to be individualised according to co-morbidities and patient preference.

Juvenile polyposis

This is a rare condition, characterised by the histologically distinctive juvenile polyp with cystically dilated tubules embedded in abundant lamina propria. The epithelium lining, the tubules and covering the surface of the polyp is normal, but when the polyps are numerous and longstanding there is a significant risk of malignancy. All the malignancies associated with the condition occur in the gastrointestinal tract, however are not confined to the colon.¹² It is inherited as an autosomal dominant condition with variable penetrance and is genetically heterogeneous. The two genetic causes defined so far are mutations in SMAD4 and BMPR1A and interestingly, both these genetic defects would be expected to disrupt the TGF (transforming growth factor) beta signalling pathway. A closely related but distinct disorder is Cowden Syndrome, due to mutations in PTEN. Although some of the polyps in Cowden Syndrome may have the histology of juvenile polyps, the majority of polyps do not. There is essentially no risk of gastrointestinal malignancy in Cowden Syndrome, which is instead associated with breast and thyroid cancer.

It is recommended that patients at risk of juvenile polyposis start having colonoscopy from age 15 or earlier if symptomatic.¹² Upper endoscopy and even capsule endoscopy should be considered, especially if there is a family history of gastric or small bowel cancer.¹³ If possible, all polyps should be removed and if they are too numerous, surgery should be considered, especially if polyps start to show dysplasia.

Peutz-Jeghers syndrome

This rare syndrome is also characterised by a particular histological type of polyp, in which there is prominent

hypertrophy of the smooth muscle layer which extends and branches up towards the epithelium, which does not usually show dysplasia. Polyps are most common in the small intestine. In addition to conferring a risk of malignancy, they are associated with acute bowel obstruction. There are extra-intestinal manifestations, including mucocutaneous pigmentation on the lips and an increased risk of breast, pancreatic, ovarian and testicular cancers.¹⁴ It is an autosomal dominant condition and in many families is due to mutation in STK11 (LKB1).

De novo mutations are common so there may be no family history. Surveillance with regular colonoscopy and endoscopy should commence in the late teens or earlier if there are symptoms. A most important aspect of management is surveillance for small intestinal polyps beyond the reach of the endoscope and capsule endoscopy, followed by push enteroscopy which has made a major contribution to better management of these patients.

Hyperplastic polyposis

This increasingly recognised syndrome is characterised by multiple (>20), large (>1cm) and proximal hyperplastic polyps.¹⁵ It is now recognised that this syndrome confers a high risk of colorectal cancer. This has prompted a review of the pathological classification of hyperplastic polyps, which were previously thought to have no malignant potential. It is now recognised that the polyps occurring in this syndrome are in fact a particular form of serrated polyp named a sessile serrated adenoma.¹⁶ This syndrome is associated with a marked tendency to hypermethylation of the CpG islands in the promoters of key cancer-associated genes. Many of the cancers have silenced MLH1 by hypermethylation of its promoter and thus show a high level of MSI. However, this condition is distinct from HNPCC (Lynch syndrome) and screening for a germline mutation in MLH1 is not productive.⁵

In many cases of hyperplastic polyposis there is no family history of polyposis or even colorectal cancer and the genetic aetiology of the condition is unclear. No predictive genetic testing can be offered at present. It seems likely that the polyps precede development of cancer by several years and it is recommended that first degree relatives be offered screening as for moderate risk families (five yearly colonoscopy from 10 years younger than the youngest affected subject in the family).⁵ Management of affected individuals is complex and clear guidelines have only recently emerged. It is recommended that sessile serrated adenomas be completely removed endoscopically and that colonoscopy be repeated every one to two years if the subject meets the definition of hyperplastic polyposis (>20 polyps).^{5,16} The risk of cancer increases if the polyps show dysplasia. In these subjects and those in whom polyps are too numerous to be safely removed during colonoscopy, colectomy and ileorectal anastomosis should be considered.

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INHERITED CANCER SUSCEPTIBILITY SYNDROMES IN PAEDIATRIC PRACTICE

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Abstract

Since the development of the "two hit hypothesis" by Alfred Knudson to explain the familial nature of cases of bilateral retinoblastoma,¹ there has been growing recognition of the inherited nature of some malignancies. This review highlights a number of paediatric presentations of inherited cancer susceptibility syndromes. In patients diagnosed with retinoblastoma, multiple endocrine neoplasia type 2, Von-Hippel Lindau syndrome, neurofibromatosis type 2 or familial adenomatous polyposis, genetic testing is now recognised as being central to the care of the patient and other family members and enables surveillance and/or prophylactic treatment to prevent some of the associated disease

The difficulty for clinicians managing families of children with paediatric tumours is to decide when to investigate for an inherited cancer predisposition, how to discuss this possibility with a family and how information from genetic testing may be helpful for the management of the extended family. Specific knowledge of the disorder and its association with a rare tumour type, such as adrenocortical tumours in Li-Fraumeni syndrome, or medullary thyroid tumours in multiple endocrine neoplasia (MEN2), may alert the clinician to this possibility. Other factors may include an increased number of cancer diagnoses in family members, the type of tumours seen, or a younger age at diagnosis. The absence of family history should not be a deterrent to referral of the family, since in many disorders, the rate of new (de-novo) germline mutations is high. The presence of multiple or bilateral primary tumours in the index case is also a helpful indicator of an inherited cancer susceptibility, for instance bilateral retinoblastoma or Wilms tumour. This review will approach the question from the point of which tumour diagnoses should prompt consideration of a familial

cancer syndrome, rather than describing each in detail.

Retinoblastoma

Retinoblastoma is a rare malignant tumour of the developing retina, typically presenting before the age of five years, with an incidence of one in 17,000. It is the most common form of ocular cancer in infancy and childhood. Tumour formation is triggered by the loss of expression of the retinoblastoma (RB1) gene-product caused by mutational events affecting both copies of the RB1 gene.² The RB1 gene is a tumour suppressor gene which has a key role in cell cycle control. In approximately 40% of cases of retinoblastoma the loss of one functional copy of RB1 gene occurs as a dominantly inherited germline mutation. This is then followed by the acquired somatic loss of the second copy of the gene within some cells in the retina. This is referred to as hereditary retinoblastoma.

Retinoblastoma can be classified in terms of family history, number of tumours and laterality (unilateral versus bilateral). All cases where there is a known family history (approximately 10%), or where the tumours

are bilateral (approximately 40% of cases), should be assumed to be due to a germline mutation in one copy of the RB1 gene. In the remaining cases without a family history, where there is a unilateral retinoblastoma, a germline mutation will be identified in 10-15% of patients. The incidence of germline mutations is greater in those individuals with multiple unilateral tumours compared to those patients with solitary tumours.

Management of the affected child includes careful screening of the proband to allow early detection of a second retinoblastoma. Screening of "at risk" family members during infancy may also be required to permit early detection of any retinoblastoma. The clinical problem is to try to separate the truly sporadic retinoblastomas from the inherited form, where relatives may be at risk. This question may be answered by performing gene mutation analysis on DNA from peripheral blood. In the case of retinoblastoma extra information may be obtained by analysis of tumour tissue from an affected child. The use of tumour tissue enables the identification of the genetic mechanisms by which both copies of the RB1 gene are inactivated in the tumour. If one of these mutations is found in peripheral blood, this confirms hereditary retinoblastoma (whether the tumour is unilateral or bilateral). Details of any germline mutation identified in the proband can then be used to allow predictive genetic testing in all at-risk family members. Conversely, if neither of the two mutations found in the tumour is identified in the proband's blood, then the tumour can be considered sporadic.

Mutation detection rates in retinoblastoma cases where there is a family history or bilateral tumours are close to 90%.^{3,4} Even in cases of unilateral retinoblastoma, the 10-15% chance of identifying an inherited mutation is sufficient to warrant testing in all new cases of retinoblastoma.

Wilms tumour

Wilms tumour has an incidence of one in 10,000. The majority of Wilms tumours occur sporadically with only 1-2% of cases having a history of another affected family member.⁵ Approximately 5% of tumours are bilateral and these cases often present a year younger than the usual age of diagnosis (three to four years).⁶ Congenital anomalies such as aniridia or genitourinary anomalies are found in 1-3% of all patients. Wilms tumour susceptibility is associated with a number of genetic disorders, most notably overgrowth disorders such as Beckwith-Wiedemann syndrome (BWS) or isolated hemihypertrophy. A recent review of Dutch paediatric cancer survivors suggested an underlying genetic diagnosis in 17% of Wilms tumour patients.⁷ Bilateral disease is more common in association with a syndromic diagnoses or other congenital anomaly and suggests a potential underlying genetic susceptibility.

The recognition of interstitial chromosomal deletions at 11p13 in patients with Wilms tumour and aniridia lead to the identification of the WT1 gene. Mutations in this gene are identified in patients with renal and genitourinary tract syndromes such as Denys-Drash syndrome and Fraser Syndrome. WT1 mutations are

rarely identified in familial cases. Two other loci have been implicated in familial cases (17q21 and 19q13). Rare cases will be associated with other tumour susceptibilities such as Li-Fraumeni syndrome. Genetic modelling in familial cases suggests complex, rather than simple mendelian inheritance.⁵

All patients with Wilms tumour should be carefully examined to identify an underlying genetic syndrome. Individuals identified with isolated hemihypertrophy, or overgrowth disorders such as BWS should be offered three monthly renal, adrenal and liver ultrasounds, until at least five years of age because of the higher risk of developing embryonic tumours. This technique has been shown to be cost-effective, allowing diagnosis at an earlier disease stage, conferring survival advantage.⁸ The presence of bilateral tumours or a confirmed family history should prompt consideration of renal screening in other "at-risk" siblings and potentially in offspring. Mutation testing of the WT1 gene may be indicated.

Gastrointestinal polyposis

The polyposis conditions may present in the paediatric age group, but will be reviewed only briefly here as further information is contained in the article by Leggett in this issue of Cancer Forum. Familial adenomatous polyposis (FAP) is the most common gastrointestinal polyposis syndrome. In 20-30% of cases there will be no known family history. In classical FAP, approximately 75% of affected individuals will develop multiple adenomatous polyps in the distal large bowel by the age of 20 and 90% by the age of 30.⁹ There are a number of other inherited polyposis disorders that present in childhood or adolescence with juvenile or hamartomatous polyps. Isolated juvenile polyps are relatively common in the paediatric age group, are identified in 1-2% of the paediatric population and do not suggest an inherited cancer susceptibility.

The classical disorder presenting with hamartomatous polyps is Peutz-Jeghers syndrome. The diagnosis of this disorder is confirmed by the presence of two or more hamartomatous polyps, which may be present at any point along the gastrointestinal tract (most commonly upper jejunum), along with characteristic oral, peri-anal or digital pigmentation, or one of these features in association with a known family history. Paediatric presentation is often with an intussusception. Juvenile polyposis is characterised by a predisposition to hamartomatous polyps in the stomach, small intestine, colon and rectum. Heterozygous germline mutations in genes such as BMPR1A, MADH4 (SMAD4), PTEN and ENG have been identified in approximately 20% of individuals with juvenile or mixed polyposis syndromes.¹⁰

Endocrine tumours

Thyroid and adrenal tumours are rare in the paediatric age group, but may be associated with a number of hereditary cancer syndromes. The multiple endocrine

neoplasias are an important group of disorders and deserve special attention. In MEN2, predictive genetic testing of children in families with this disorder is a crucial part of their management, allowing currently asymptomatic mutation carriers to have a prophylactic thyroidectomy in infancy or early childhood, to minimise the risk of developing an aggressive medullary thyroid cancer. This has become the paradigm for patient management in other hereditary cancer syndromes.

There are two types of multiple endocrine neoplasia syndrome (MEN1 and MEN2) associated with a susceptibility to a number of different tumours, each with a prevalence of around one in 20,000. These two syndromes are explained by inherited mutations in two genes, MEN1 (locus on 11q13) in the MEN1 and RET (10q11) in the MEN2 syndrome.^{11,12}

A practical definition of MEN1 includes any individual with two of the three following features – parathyroid adenomas, entero-pancreatic tumours and pituitary tumours.¹³ There may be other families where there are features that are suspicious of this disorder, but who do not fulfill this definition. Mutation testing and clinical surveillance may still be warranted in such families. The earliest and most common clinical feature in patients with MEN1 is hyperparathyroidism due to multiglandular hyperplasia. Many MEN1 patients have evidence of this in their 20s, with over 95% being affected by the age of 40. This is significantly earlier than for patients with sporadic parathyroid adenomas/hyperparathyroidism. The most prevalent tumours associated with MEN1 are gastrinomas (40% of patients), insulinomas (10% of patients) and pituitary adenomas particularly prolactinomas (20% of patients).¹³

MEN2 is a disorder characterised by a high risk of developing medullary thyroid cancer. The disorder is divided into three clinical categories – MEN2A, MEN2B and familial medullary thyroid cancer (FMTC). Patients with MEN2A are at risk of developing parathyroid adenomas and pheochromocytomas, as well as medullary thyroid cancer. MEN2B patients are also at increased risk of pheochromocytomas, but not typically parathyroid tumours. Patients with MEN2B are defined by their phenotypic features, which include a marfanoid habitus, mucosal neuromas and intestinal ganglioneuromatosis. They are at high risk of developing aggressive medullary thyroid tumours, often at a very young age. FMTC is defined by the absence of other associated endocrine tumours in families with multiple affected individuals. Medullary thyroid tumours have a peak age of presentation of 55 years and their diagnosis in paediatric practice is almost always associated with a diagnosis of MEN2.

Pheochromocytomas presenting in childhood are rare in MEN2. They are more commonly associated with Von-Hippel-Lindau syndrome (VHL), especially where they present as bilateral tumours in this age group. In a population series of apparently sporadic pheochromocytomas, 59% of cases diagnosed under the age of 18 years were associated with an underlying tumour susceptibility syndrome.¹⁴ The presence of extra adrenal disease suggests an hereditary paraganglioma syndrome due to mutations in genes involved in the

succinate dehydrogenase complex (SDHB and SDHD). All children presenting with pheochromocytomas should be carefully evaluated for these disorders. Clinical assessment should include screening for VHL associated lesions in a patient's eyes, spinal cord and cerebellum.

Li Fraumeni Syndrome

Li Fraumeni Syndrome (LFS) is a high penetrance cancer predisposition syndrome, classically defined by the presence of sarcoma with other early onset cancers in three closely related individuals. Those cancers reported to be particularly associated with the syndrome include early onset breast cancers, soft tissue and bone sarcomas, brain tumours, leukaemia and adrenocortical carcinoma, as well as germ cell tumours, stomach cancer, melanoma and Wilms tumour.^{15,16} LFS is associated with a lifetime cancer risk of up to 85%, with more than half of the malignancies occurring prior to the age of 30 years.¹⁷ The syndrome is typically caused by dominant mutations in the p53 gene (locus 17p13).¹⁸

A diagnosis of LFS should be considered in any individual with two paediatric malignancies, or adrenocortical tumour or sarcoma, in association with a family history of other early onset cancers. In one series, 80% of patients with adrenocortical tumours had a germline p53 mutation, although the mutations seen in association with these tumours often have a low penetrance in terms of increasing the risk of developing other LFS associated tumours.¹⁹ Although efficacy of screening of at-risk relatives for the associated cancers may be limited, given the range of possible tumours, knowledge of this cancer predisposition may alter management decisions and may preclude the use of radiotherapy.

Neurogenetic tumours

The classic neurogenetic syndromes presenting with tumours in the paediatric age group are Neurofibromatosis type 1 (NF1) and type 2 (NF2). These disorders are aetiologically and clinically distinct, although at one time their similar cutaneous features may have led to some confusion in separating the phenotypes. NF1 is far more common with an incidence of about one in 3000-4000. The diagnosis is confirmed by identifying a characteristic combination of cutaneous, ocular and skeletal features. Common complications include learning, growth and ocular abnormalities. Optic glioma are detected in 9.6% of NF1 patients, although in most cases they remain clinically asymptomatic and may often regress in adult life.²⁰ Individuals with NF1 also have an increased risk of developing other CNS tumours, pheochromocytomas, leukaemias and other myelodysplasias, however these are still rare in this group, each occurring in < 2% of patients.²¹

Neurofibromatosis type 2 (NF2) is a rare, dominantly-inherited susceptibility to tumours of the central nervous system, in particular acoustic neuromas, meningiomas and schwannomas. The incidence of NF2 is estimated

from the United Kingdom NF2 registry to be one in 37,000. The presence of bilateral acoustic neuromas (schwannomas) is pathognomonic of NF2, although a single early onset acoustic neuroma, combined with other features such as schwannomas, meningiomas or juvenile cataracts, may be diagnostic.²² Complications related to an acoustic neuroma, such as deafness, tinnitus and balance disturbance, are common presenting symptoms in NF2. Other complications include cataracts, typically posterior pole cataracts (81%), meningioma (49%) and spinal cord lesions (67%).²³ Typical age of presentation is between 18 and 24 years of age.²³ Paediatric presentations are likely to relate to meningiomas or schwannomas.²⁴ Any child presenting with a schwannoma or meningioma should be investigated for evidence of other signs of NF2.

Between 10-40% of spinal cord and cerebellar haemangioblastomas are associated with a diagnosis of VHL syndrome. These lesions should always prompt investigation for other features of this disorder, especially if the presentation is at a young age.²⁵ Familial clusters of brain tumours, particularly medulloblastomas or glioblastoma multiforme, have occurred in association with gastrointestinal polyposis in Turcot's syndrome. Reported cases in the paediatric age group typically present with medulloblastomas and a significant proportion of patients with this rare syndrome have been found to have APC mutations.²⁶

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HEREDITARY DIFFUSE GASTRIC CANCER: A REVIEW

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Abstract

Hereditary diffuse gastric cancer is caused by a germline mutation in the CDH1 gene. Individuals found to carry a CDH1 mutation are at a significantly increased risk of diffuse type gastric cancer, as well as an increased risk of lobular type breast cancer for females. This review outlines the criteria for a clinic diagnosis of hereditary diffuse gastric cancer and indications for genetic testing. The management options for CDH1 mutation carriers include surveillance by chromo-endoscopy, or prophylactic gastrectomy. These management options will be addressed including a discussion on their

Case history

A germline CDH1 mutation was identified in a 39 year old woman diagnosed with signet ring cell gastric cancer. The only significant family history was that her

sister was diagnosed with gastric cancer at the age of 20. Both women are now deceased. The identification of this mutation confirmed the diagnosis of hereditary diffuse gastric cancer in the family.

This finding raises significant issues for at-risk family members, including whether or not to take up predictive testing, the age at which predictive testing should be offered to children and then the management options for those found to carry the mutation, such as endoscopic screening or preventative gastrectomy. Hereditary Diffuse Gastric Cancer (HDGC) is a rare condition. Genetic testing can be helpful in clarifying risks and management for other family members.

Genetic susceptibility to gastric cancer

The incidence of gastric cancer in Australia per 100,000 people was 14.3 and 5.5 among males and females respectively in 2004.¹ This accounts for approximately 2000 people being diagnosed with gastric cancer per year within Australia.² Of all gastric cancers, approximately 5-10% show familial clustering, with two or more cases in the same family.³ However, only 1-3% of all gastric cancers occur in families with autosomal dominant gastric cancer susceptibility.^{4,5}

A single gene has been identified with a causative role in HDGC, the CDH1 gene, encoding the protein E-Cadherin. Germline mutations in the E-cadherin gene cause an increased risk of diffuse type gastric cancer and lobular breast cancer.⁶ In a recent population based study of 81 patients with gastric cancer (diagnosed under the age of 50) and unselected for family history, the frequency of CDH1 mutations was 1.2% (1/81).⁷ Germline mutations in the mismatch repair genes, causing hereditary non-polyposis colorectal cancer (HNPCC), lead to an increased risk of intestinal type gastric cancer.⁸ There is also an increased risk of gastric cancer associated with other inherited cancer predisposition syndromes, including Peutz Jeghers syndrome,⁹ familial adenomatous polyposis¹⁰ and Li-Fraumeni syndrome.¹¹

In 1998, the CDH1 gene was identified by genetic linkage analysis as a candidate gene within several large Maori families with early onset autosomal dominant diffuse gastric cancer.¹² Sequencing revealed germline CDH1 mutations in the three families. A study of 18 gastric cancer families of European descent (England, Italy, Portugal) also found CDH1 mutations in three families with diffuse type gastric cancer.¹³ In 1999, a further six CDH1 mutations were identified in families of mixed ancestry with diffuse type gastric cancer,¹⁴ confirming that a germline mutation in CDH1 is a common determinant of a dominantly inherited susceptibility to diffuse gastric cancer.

In 1999, the International Gastric Cancer Linkage Consortium (IGCLC) was established with the aims of developing common terminology for the disease and to produce evidence-based management guidelines.¹⁵ In formulating a definition of familial gastric cancer syndromes, a distinction was made between the different histopathological sub-types of gastric cancer (intestinal, diffuse or mixed/diffuse with glandular component) that segregate within families. The IGCLC initially defined

the criteria for a clinic diagnosis of HDGC as any family fulfilling one or more of the following:

- Two or more documented cases of diffuse gastric cancer in first or second degree relatives, with at least one diagnosed under the age of 50.
- Three or more cases of documented diffuse gastric cancer in first or second-degree relatives, independent of age.

Based on the limited data available at that time, the IGCLC predicted up to 25% of families that met the criteria for HDGC would have a CDH1 mutation.¹⁵ Since then, CDH1 mutations have been identified in approximately 30-40% of HDGC families, fulfilling the IGCLC criteria.¹⁶ In response to concerns that the criteria may be too stringent, revised criteria were established and assessed in a second study of 42 HDGC families.¹⁷

The six revised criteria were any family fulfilling one or more of the following:

- Two or more cases of gastric cancer in a family, with at least one diffuse gastric cancer diagnosed before age 50 years.
- Three or more cases of gastric cancer in a family, diagnosed at any age, with at least one documented case of diffuse gastric cancer.
- An individual diagnosed with diffuse gastric cancer before 45 years of age.
- An individual diagnosed with both diffuse gastric cancer and lobular breast cancer (no other criteria met).
- One family member diagnosed with diffuse gastric cancer and another with lobular breast cancer (no other criteria met).
- One family member diagnosed with diffuse gastric cancer and another with signet ring colon cancer (no other criteria met).

The second study found CDH1 mutations in 48% (12/25) of families meeting Criteria 1, but only 5.5% (1/18) of those meeting the less stringent criteria. The conclusion was that families with a CDH1 mutation are those with a strong family history of early onset diffuse gastric cancer, and therefore Criteria 1 provides the best guide for CDH1 mutation screening.¹⁷ This study also indicated that a single individual with early onset diffuse gastric cancer, without a family history, is unlikely to carry a CDH1 mutation.

Several other studies have examined the frequency of E-cadherin germline mutations in patients with early onset gastric cancer (diagnosed before the age of 45 years) without a family history, in populations with a low incidence of gastric cancer. The overall reported frequency of cases diagnosed under 50 years that are attributable to E-cadherin mutations is about 1%.⁷ Screening for CDH1 germline mutations in individuals

without a family history should therefore be limited to those early onset cases diagnosed before the age of 35.⁷

The CDH1 gene is located at 16q22.1 and consists of 16 exons covering approximately 100kb of genomic DNA encoding the E-cadherin protein.¹⁸ CDH1 mutations are dominantly inherited. So far 439 families with aggregation of gastric cancer have been analysed for CDH1 mutations, with 56 (12.8%) families having been found to carry a CDH1 germline mutation (50 distinct mutations).¹⁹ The majority are truncating mutations (80.4%), with pathogenicity caused by down-regulation or inactivation of protein expression. Missense mutations have also been identified (19.6%), however functional impact of missense mutations is difficult to predict.¹⁹ One hundred and eighteen families fit the IGCLC criteria for HDGC (26.9%); of these, 43 have had mutations identified (36.4%).¹⁹ There have been no 'hot spots' identified, with mutations dispersed along the full sequence of the gene. There have been at least 18 sequence variants identified.

The E-cadherin protein is a member of the cadherin family of adhesion molecules, which are transmembrane glycoproteins mediating calcium dependent cell-cell adhesion.²⁰ E-cadherin is a tumour suppressor gene, therefore inactivation of CDH1 in hereditary diffuse gastric cancer requires the somatic inactivation of the wild type allele, as predicted by the Knudson two-hit hypothesis. The first hit in HDGC is the germline mutation. In sporadic diffuse gastric cancer there is an initial somatic mutation. The second hit is then usually due to one of the following mechanisms: silencing of the gene by promoter hypermethylation, somatic mutations or loss of heterozygosity affecting wild type copy.²¹ Abolishment of the E-cadherin function induces loss of adherens junctions and impairment of the cell adhesiveness and cell proliferation signalling pathways.²² Tumour cells with abolished E-cadherin expression demonstrate abnormal morphogenesis and architecture of epithelial tissue, loss of cellular polarity and contact inhibition, unregulated growth and invasion of adjacent tissues.²²

Cancer (and other risks) in carriers of a CDH1 mutation

Germline mutations in the CDH1 gene cause a greatly increased risk of diffuse gastric cancer and an increased risk of breast cancer (of the lobular subtype).

Lifetime penetrance of gastric cancer, based on the original three Maori families, was estimated at 70%.¹² A penetrance analysis of E-cadherin mutations in 11 families was used to estimate the cumulative risk of both gastric and lobular breast cancer.⁶ The cumulative risk of gastric cancer by age 80 was estimated at 67% for men (95% CI, 39-99) and 83% for women (95% CI, 58-99). Ascertainment bias may have resulted in higher penetrance estimates than those obtained from

population-based studies. The age of onset is variable, ranging from 14 to 69 years, with the mean age at diagnosis between 31-51 years.¹³

The cumulative risk of lobular breast cancer by age 80 for women with a germline CDH1 mutation has been estimated at 39% (95% CI, 12-84), with the combined risk of gastric and breast cancer in women by age 80 around 90%.⁶ Signet ring cell carcinomas of the colon, prostate and ovarian cancers have been observed in HDGC families.^{17, 19, 23} However, there is no evidence of a significantly increased risk of these cancers, beyond the population risk. Cleft lip, with or without cleft palate, has been described in two HDGC families.²⁴ As cell adhesion molecules are considered to play a major role in craniofacial morphogenesis, germline CDH1 mutations may contribute to clefting.

There are some general risk factors associated with in an increased risk of gastric cancer which include gastritis and *Helicobacter pylori* infection. It is possible *H. pylori* as well as dietary and environmental factors may modify the disease risk in HDGC patients. *H. pylori* is associated with an increased risk for both intestinal and diffuse GC, however *H. pylori*-associated pre-neoplastic lesions are usually a feature of intestinal gastric cancer, not diffuse gastric cancer.⁸ Intestinal type cancer is more often related to environmental exposures, including diet (particularly salted fish/meat and smoked foods), cigarette smoking and alcohol.

Management of carriers of CDH1 gene mutation

The five-year survival rates for all gastric cancer remains low in Western countries, ranging from 20-45%.²⁵ The poor prognosis is mostly attributable to the late stage at presentation and diagnosis. Once a diffuse gastric cancer is symptomatic, it is lethal in 80% of cases.⁸ However, if detected early and resected before invasion through the gastric wall, there is a 90% five-year survival rate (regardless of histological type).²⁶ Effective management of HDGC, requires intensive clinical surveillance with the aim of identifying early gastric cancers or consideration of risk reducing strategies. For individuals with a germline CDH1 mutation, the therapeutic options currently available are either endoscopic surveillance or prophylactic gastrectomy.

The recommendations for surveillance from the IGCLC is an endoscopy every six months, performed by a team experienced at diagnosing early gastric cancer, including multiple biopsies of gastric mucosa.²³ Chromo-endoscopy with congo red-methyl blue may provide improved surveillance. In a recent study of 33 CDH1 mutation carriers, chromo-endoscopy detected 23 early signet ring cell carcinoma foci in 10 patients, which were not visible with standard white light endoscopy.²⁷ The efficacy of endoscopic surveillance is unproven. The difficulties in detecting diffuse gastric cancer are due to the lesions tending to spread in the submucosa

(beneath morphologically normal mucosa), rather than as exophytic masses, which makes them difficult to identify. Finally, it would appear reasonable to recommend *H.pylori* eradication treatment, in an effort to minimise exposure to other gastric carcinogens.²³

In two studies examining prophylactic gastrectomy specimens from CDH1 mutation carriers, all patients were found to have multi-focal signet ring cell (SRC) carcinoma, with the number of distinct foci as high as 161.^{28,29} This finding has been supported with the histopathological mapping of an additional 20 gastrectomy specimens from 4 HDGC kindred, where all stomachs had multiple foci of SRC carcinoma, with the mean number of foci approximately 100/stomach (range 4-487).³⁰ In the earlier two studies, standard white light endoscopy and multiple biopsies had failed to detect the cancers in all cases. The early invasive cancers were spread throughout the entire stomach, not isolated to a particular region.

These studies suggest there may be a significant risk reduction for CDH1 mutation carriers by undergoing a prophylactic gastrectomy. It is suggested this surgery should be performed by centres performing at least 25 gastrectomies per year, resulting in a surgical mortality of less than 5%.¹⁵

Prophylactic gastrectomy must be considered in the context of the morbidity, mortality and long-term consequences. Total gastrectomy is associated with a 2-4% risk of mortality, 10-20% risk of post-operative complications and 100% risk of long-term consequences.^{22,27} The long-term implications affect nutritional status, with possible side-effects including weight loss, lactose intolerance, fat mal-absorption and steatorrhoea, dumping syndrome, bacterial overgrowth, postprandial fullness and vitamin deficiencies.³¹ Although the severity and degree of complications are well described in older gastric cancer patients (60-70 years), this has not been evaluated in young individuals (without coexisting morbidity). However, almost all the reported patients who have undergone gastrectomy have experienced one or more of the above symptoms.²² Prophylactic gastrectomy may lead to a significant decrease in quality of life.

Finally, women with a CDH1 mutation are recommended to commence annual mammography from the age of 35, or five years younger than the age at which the youngest person in the family was diagnosed with breast cancer.³²

Conclusion

Germline mutations in the CDH1 gene are present in almost 50% of families with multiple cases of gastric

cancer, including at least one documented case of diffuse type gastric cancer diagnosed under the age of 50. Individuals found to carry a germline CDH1 mutation have a significantly increased risk of gastric cancer and data is supportive of an increased risk of lobular breast cancer for women carriers. Overall, current data suggests that standard endoscopic screening is insufficient to detect gastric cancers, therefore prophylactic gastrectomy may be recommended. For those CDH1 mutation carriers who choose not to proceed with prophylactic gastrectomy, chromo-endoscopy provides improved surveillance.²⁷

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FAMILIAL ASPECTS OF HAEMATOLOGICAL MALIGNANCY

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Abstract

The study of inherited predisposition to cancer provides the unique opportunity to identify key driver genes in oncogenesis that are likely to play important roles in the more common sporadic forms of disease. Inherited predisposition to malignancies, such as colon, breast and ovarian cancer have been well established. It has also long been accepted that several inherited syndromes, such as Fanconi Anaemia, are associated with an increased risk for haematological malignancy. However, inherited predisposition to a purely haematological malignancy, without associated syndromic features, has only recently become widely accepted. To date, only three genes have been shown to be causative of these predispositions, however in the majority of families studied, the causative mutation remains elusive. The Australian Familial Haematological Cancer Study is strategically identifying and collecting Australian families with inherited predisposition to a specific haematological malignancy. The identification and study of these families is integral to the study of haematological malignancy, as knowledge of the gene/s mutated and the subsequent disease progression in affected individuals will provide important insight into the mechanisms of

Cancer results from an accumulation of genetic mutations in genes involved in regulating cell differentiation and proliferation, leading to aberrant control of these processes. These mutations generally occur as somatic mutations due to intrinsic errors in DNA replication and ineffective repair mechanisms. However, in some rare cases, a mutation in one of these genes may occur in the germline and become a heritable mutation. It is likely that these genes, through their ability to predispose to cancer, play a key role in the development of cancer sporadically. Their identification will provide insight into the more common sporadic cases.

Familial clustering of cancer, including haematological malignancies, has been recognised by some and argued over by others for more than 50 years. Two doctors on different sides of the world, Henry T Lynch in Nebraska, United States and Frederick W Gunz, in Christchurch, New Zealand, were among the early supporters of a strong familial genetic component to cancers in the 1960s. The underlying genetic causes have subsequently been identified in a number of familial cancers, in particular the mismatch repair genes eg. MLH1 and MSH2 in colorectal cancer, and BRCA1 and BRCA2 in breast and ovarian cancer. Indeed, Lynch syndrome is a commonly used synonym for hereditary non-polyposis colorectal cancer. Many colon and breast cancer families used in the identification of these genes were collected by the ever active Dr Lynch.¹

Fred Gunz will be well known to readers of Cancer Forum as the director of medical research at the Kanematsu Institute in Sydney from 1967 until 1980 and, until his death in 1990, an active contributor to Cancer Forum. Fred Gunz is the first author on one of the few papers online today from the period and summarises the early arguments in the medical literature about a hereditary component to haematological malignancies.² Familial clustering of purely haematological malignancies has also been described, including a beautiful description by Fred Gunz and colleagues of the largest ever published

family with a predisposition to develop leukaemia, with 17 affected family members from Sydney.³

However, only three genes have been definitively identified as playing a role in these haematological malignancy predispositions.

The difficulty in identifying haematological malignancy predisposition genes partially results from an inability to perform linkage studies. This is due to relatively small family sizes, the high mortality rate, incomplete penetrance, relatively late age of onset and potential for sporadic phenocopies. A greater number of genes has been identified in bone marrow failure syndromes or other syndromes where an increased risk for haematological malignancy exists, however a number of non-haematological diseases/phenotypes are also observed.

Pure familial leukaemia

A large number of families has been described in the literature, where aggregation of a greater than expected number of individuals diagnosed with a particular type of haematological malignancy has been observed. Lowenthal et al documented a series of over 200 pedigrees with two or more cases of haematological malignancies between 1972 and 1980.^{4,5} Some of these pedigrees are large, with 12 or more affected individuals in the one family. It has also been observed that there is a propensity for individuals within the same family to be afflicted with a disease showing similar clinical phenotype. For example, families exist where predominantly acute myeloid leukaemia (AML) is observed, whereas others exist where only chronic lymphocytic leukaemia (CLL) is found, suggesting that the gene/s affected are distinct between the different

families. Inheritance patterns also suggest many families have monogenic disorders displaying autosomal dominant inheritance, with varying penetrance.

Familial chronic lymphocytic leukaemia (CLL)

CLL is the most common form of sporadic leukaemia in western countries, representing approximately 30% of all cases. CLL also appears to show a relatively common familial aggregation, with some epidemiological studies suggesting a three-to-seven fold increased risk in first degree relatives of a CLL patient.^{6,7} More than 80 families showing CLL aggregation have been reported.⁸ This includes an Australian family with at least 12 affected members over four generations, ascertained by James Wiley, Professor of Haematology, University of Sydney and at least partially responsible for a linkage signal on chromosome 11p11.⁹ In 1975, Gunz and colleagues reported on a study of 909 families in respect to familial leukaemia.¹⁰ They reported that first degree relatives with leukaemia were much more frequent in families of patients with chronic lymphocytic, than in those of patients with chronic granulocytic leukaemia. The incidence of leukaemia among first degree relatives was established to be 2.8 – 3.0 times, among more distant relatives about 2.3 times and overall about 2.5 times that expected. Subsequently, a 1984 Tasmanian study found that 11.8% of CLL cases had at least one affected first degree relative.⁴

Several large association studies have been performed on cohorts of CLL families leading to the identification of several candidate loci, including 11p11,⁹ 13q21.33-q22.2¹¹ and 6p21,^{3,12} however no genes in these regions have been implicated to date. Regions of consistent chromosomal rearrangement in sporadic CLL have also been suggested, such as consistent deletion of 13p14.3, implying the presence of a tumour suppressor gene.¹³ No genes within these regions have been implicated, although recently a common nonsense polymorphism in the ARLTS1 ADP-ribosylation factor gene in the 13p14.3 commonly deleted region was found to be associated with familial CLL.¹⁴ However, several groups have since been unable to confirm this result in their own familial cohorts.^{15,16}

In a paper recently published in Cell, an epigenetic and genetic mechanism for CLL predisposition in a family ascertained by Henry Lynch with seven affected individuals was proposed.¹⁷ The authors found significant linkage to 9q21-22 in this family and sequencing of the region identified a novel regulatory sequence change in the death-associated protein kinase, DAPK1 gene, in all affected members analysed.¹⁷ This sequence change correlated with significant down-regulation of DAPK1 expression in these individuals. The same authors demonstrated that DAPK1 is epigenetically silenced in 89% of sporadic CLL, thus reduced expression of this gene appears to be a potent promoter of CLL formation.¹⁷ While it has not been definitively proven that DAPK1, or this sequence variation, is causative of CLL in this family, the data signifies the potential for regulatory mutations to play a role in familial cancer. It also shows that DAPK1, like the other two known familial haematological malignancy genes, RUNX1 and CEBPA, is important in both familial and sporadic haematological malignancies (see below).

Lymphoproliferative disorders – non-Hodgkin lymphoma

and Hodgkin lymphoma

Several studies utilising large Swedish and Danish cancer registries have identified significant familial aggregation of the lympho-proliferative disorders, non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL).¹⁸⁻²⁰ The 1984 Tasmanian study by Giles et al identified 13 potential families (at least two affected first degree relatives) with NHL and found that the overall risk for first degree relatives of an affected individual was 3.15-3.61.⁴ However, no chromosomal regions or candidate genes have yet been implicated.

Acute leukaemia

Families with acute lymphocytic leukaemia (ALL) have been reported^{21,22} and a significant number of families with predisposition to AML have been described.²³ Families with aggregation of AML can be broadly segregated into those with a pre-leukaemic familial platelet disorder (FPD-AML), those with a pre-leukaemic early onset myelodysplasia (MDS-AML) and those with no obvious pre-leukaemic phenotype (AML). Clinically, this pre-leukaemic phase allows identification of “potentially unaffected” siblings for genetic testing and allogeneic bone marrow donation. The gene responsible for most, if not all cases of FPD-AML, has been identified as has one gene for familial AML. No gene has been identified for a number of other familial AML cases, or for MDS-AML cases, however one region on 16q22 has been implicated in MDS-AML.

The FPD-AML gene, RUNX1, is present on 21q22.1 and is one of the most frequent targets of chromosomal aberrations in sporadic AML and point mutations, deletions and amplifications have also been identified.^{24,25} Germline RUNX1 mutations have been found in 12 families with FPD-AML.²⁶⁻³¹

The other identified familial AML gene, CEBPA, lies on 19q13.1 and is mutated in approximately 9% of sporadic AML.³² Germline mutations were recently identified in two families with AML and accompanying eosinophilia, but with no obvious pre-leukaemic phenotype.^{33,34} These two germline mutations affecting the same polyC string, appear to cause a truncation of the normal 42kDa protein resulting in increased formation of the 30kDa dominant negative isoform, which inhibits DNA binding and transactivation by wild-type CEBPA.^{33,34} We have recently identified (unpublished data) similar mutations in the Sydney pedigree described by Fred Gunz et al.³ An unexpected observation in this pedigree is that affected carriers of the mutation have an extremely poor clinical outcome compared to the two other published pedigrees, in which some patients were treated in the 1960s and clinical outcome was excellent.

The chromosomal region 16q22 was found through candidate region linkage analysis to be linked with disease in two families with MDS-AML.³⁵⁻³⁷ The gene for the integral cofactor of RUNX1 and CFBF lies within this region, however pathogenic mutations in this gene and several other neighbouring candidate genes have been ruled out in both families.^{38,39}

There still remains a large number of families reported in the literature in which no causative mutation has been identified.

Syndromic predisposition to leukaemia

Several inherited syndromes also confer an increased risk of haematological malignancy, however a number of other disease characteristics are also present. These syndromes result from mutations in genes whose key functions are not confined to the haematopoietic system, and are thus less likely to represent key haematological malignancy driver genes in sporadic cases. However, insight into oncogenesis may still be gained through identifying how these genes lead to an increased risk of haematological malignancy.

Specific syndromes are outlined in Table 1, however a general overview of the different groups of syndromes is given below.

Table 1

Gene	Syndrome	OMIM#	Inheritance	Haematopoietic malignancies*	Approximate risk*
DNA repair syndromes					
ATM	Ataxia telangiectasia	208900	Autosomal recessive	T-cell lymphoma, T-ALL, T-PLL, B-cell lymphoma	12%
BLM	Bloom syndrome	210900	Autosomal recessive	AML, ALL, lymphoma	25%
FANC (A, B, C, D1, D2, E, F, G, J, L, M, N)	Fanconi anemia	227650	Autosomal recessive	AML	10%
NBS1	Nijmegen breakage	251260	Autosomal recessive	Lymphoid	Unknown
Bone marrow failure syndromes					
ELA2, GFI1, HAX1	Severe congenital neutropenia, Kostman	251260	Autosomal dominant, autosomal recessive	AML, AMoL	2-10%
SBDS	Schwann-Diamond	260400	Autosomal recessive	ALL, AML, AMML, AMoL, EL, JMML	5%
Linkage to 19q or 8p (80%) or RPS10 (20-25%)	Diamond-Blackfan	105650	Autosomal recessive and dominant	AML	4%
Tumour suppressor syndromes					
TP53	Li-Fraumeni	151623	Autosomal dominant	B-CLL, ALL, CML, HL, BL, JMML, AML	50% for all cancers
NF1	Neurofibromatosis	162200	Autosomal dominant	JMML, AML	350-fold increase
Immunodeficiency syndromes					
ADA	Severe Combined immunodeficiency	102700	Autosomal recessive	B-cell lymphoma	5%
WASP	Wiskott-Aldrich (WAS)	301000	X-linked recessive	ALL, HL	7%
CD40L	X-linked immunodeficiency	308230	X-linked recessive	Lymphoma, HL	Unknown
SAP	X-linked lymphoproliferative (XLP)	300635	X-linked recessive	EBV-related B-cell lymphoma	20%
http://www.ncbi.nlm.nih.gov/sites/entrez?db=OMIM			*Adapted from ref.23		

DNA repair syndromes

Autosomal recessive mutations leading to DNA repair deficiency have been shown to predispose to cancer, particularly haematological malignancies. Such syndromes include Ataxia Telangiectasia, Fanconi Anaemia and Li Fraumeni syndrome.

Bone marrow failure syndromes

Bone marrow failure syndromes show defects in several hematopoietic lineages and include Kostmann syndrome of severe congenital neutropenia, Shwachman Diamond syndrome, dyskeratosis congenital and Diamond-Blackfan anaemia. All of these syndromes strongly increase the risk of acquiring MDS and leukaemia.⁴⁰

Immuno-deficiency syndromes

Some immuno-deficiency syndromes have also been linked to an increased risk of haematological malignancy, however it is still unknown how these syndromes predispose to malignancy. These syndromes include severe combined immuno-deficiency disease, Wiskott-Aldrich syndrome and X-linked lymphoproliferative syndrome. All have been shown to predispose to B-cell lymphomas.

Australian Familial Haematological Cancer Study (AFHCS)

The only systematic familial collection of haematological malignancies is being performed by Henry Lynch in the US, whose collection has many families with multiple myeloma, and Richard Houlston at the Institute of Cancer Research in the United Kingdom, whose collection of families with at least one case of CLL and other haematological malignancies is being utilised to identify familial CLL genes. The AFHCS was established to systematically collect Australian families with all types of haematological malignancies.

The AFHCS represents a powerful collaboration between researchers, nurses, haematologists and oncologists, enabling families to be identified, pedigrees assessed and relevant affected and unaffected samples to be efficiently collected. Collection criteria includes affected sibling pairs, parent child transmission and/or three first degree relatives. This approach has already identified 24 families with apparent predisposition to haematological malignancy. Calculations based on this rate of collection within South Australia alone have suggested that at least 200 such families may exist within Australia. The families collected thus far include CLL, AML, HL and NHL families, as well as mixed haematological malignancy families.

Our preliminary data does not support the fact that familial haematological malignancies are rare. Indeed, similar to other cancers, we would propose that 5-25% of haematological malignancies will be caused by either highly penetrant germline mutations (5-10%), or will show 'familial' clustering due to lower penetrance germline mutations and/or gene-environment interactions (10-15%). Our database shows 124 Australians with familial haematological malignancies and we have identified RUNX1 and CEBPA mutations in 36 Australian patients from three families, including many at-risk individuals. This information has already been used in the choice of bone marrow donors.

The power of this approach is the ability to identify families and subsequently recruit a large number of relatives of the pro-band, both affected and unaffected, into the study. Close collaboration with the admitting hospitals also enables collection of affected pathology samples, which reduces the confounding effect of the high mortality of these diseases on linkage power. Linkage remains the most powerful method for monogenic disease gene identification and the AFHCS provides a unique opportunity to obtain enough samples to allow powerful linkage to be performed.

Conclusion

The prevalence of familial predisposition to haematological malignancy is becoming increasingly apparent. To date, it has not been properly studied. Whilst many syndromes increase the risk of leukaemia or lymphoma, there are increasing numbers of purely haematological familial predispositions being identified due to increased awareness among clinicians. The variety of haematological malignancies represented by these families, for example AML, CLL and HL, suggests that a number of distinct haematological malignancy driver genes await discovery.

Currently, disease gene identification in families with haematological malignancy predisposition is confounded by an inability to perform linkage analyses. Collaborative efforts such as the AFHCS represent a potential solution to this problem through their systematic and efficient collection of families, where samples from a number of affected and unaffected individuals are available (including pathology samples).

It is hoped that identification of these familial haematological malignancy genes will identify novel players in the more common sporadic forms of the disease. Subsequent studies on the downstream events occurring during disease progression in these families, will aid in the elucidation of the mechanisms of both familial and sporadic haematological malignancy, as well as the discovery of novel therapeutics and diagnostics.

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THE CANCER COUNCIL AUSTRALIA'S STUDENT ESSAY COMPETITION

The Cancer Council Australia's annual essay competition is open Australian residents enrolled in a medical course in an Australian university. Students are required to submit an essay on an issue related to cancer control. In 2007, the topic was cancer care across cultures. The essays are judged by members of The Cancer Council Australia's Oncology Education Committee.

This article is the winning essay by Abhishek Kumar Verma. As the winner, Abhishek attended the World Health Organisation's Collaborating Centre for Cancer Education's International Summer School 'Oncology for Medical Students' in Vienna in July 2007.

UNDERSTANDING AND MANAGING CANCER NEEDS THROUGH THE KALEIDOSCOPE OF CULTURE

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Abstract

The experience of cancer and attitudes of patients towards this disease is based-on and profoundly influenced by a patient's cultural and social beliefs. A 'one approach fits all' model of clinical diagnosis and treatment does not meet the varying cultural, spiritual and social needs of contemporary western societies. Traditional western approaches of disclosure and individual decision making can become obstacles in the effective management and treatment of cancer. Models can be adapted and developed to suit the local context of diverse populations. Understanding the significance of cultural factors and harnessing these to develop culturally sensitive cancer management strategies is crucial in using

"The diagnosis of cancer induces a human dread that is grounded in our biological being. Nevertheless, the experience of cancer and its treatment is inevitably influenced by cultural, ethnic, economic and religious differences."¹

The significance of cultural context in cancer care has been demonstrated by many studies. As the cognitive framework of collective and individual world views, culture shapes how patients react to, cope with and make decisions about the management of their cancer. Given Australia's diverse cultural heritage and that cancer is the major cause of death in Australia,² understanding cultural influences on cancer across the world and in our own society is imperative.

The first section of this essay will analyse how cultural determinants influence patients' perceptions of cancer,

while the second section will review the framework needed for culturally sensitive cancer management approaches, as well as some established and emerging strategies for addressing the cancer care needs of diverse populations.

The impact of cultural perceptions of cancers

"A better understanding of common problems across cultures as well as salient cultural differences can only improve the standard of cancer care in many cultures."³

According to Intercultural Cancer Council of America statistics, Chinese-American communities experience the highest mortality rate for liver cancer, while Filipinos suffer a higher incidence of thyroid cancer.⁴ Vietnamese women have two and a half times higher rates of cervical

cancer than any other cultural community in America. In Australia, incidence rates are high for cancer of the liver, lung and cervix for Indigenous Australians,⁵ while other cultural groups such as Chinese Australians or Greek Australians suffer from high rates of stomach cancer. Attempts to address cancer care needs in these groups have demonstrated that despite some acculturation, the culturally held beliefs of different groups about hierarchy systems, spiritual concepts, significance of family and decision making dynamics, are still fundamental in shaping individual reactions to cancer. These beliefs can vary dramatically between cultural groups. Differences in the cultural world of doctor and patient may mean disparate and even conflicting frameworks of illness and disease. Hence, "the effectiveness of the medical encounter, including the ability to communicate in increasingly diverse cultural and bio-medical contexts, can be especially problematic in the field of oncology".³ Overseas studies have illustrated that African-American women perceive cancer as inevitably fatal,⁶ Bangladeshi groups in the UK had poor information about cancer⁷ and understanding of the extent of cancer and the probability of recovery was poorer in non-English speaking patients than English-speaking ones in North American cancer centres.⁸

Closer to home, there have been similar findings about cancer and the experience of this disease in multicultural communities within Australia. A 2002 study by Goldstein et al found that many Greek Australians perceived a cancer diagnosis as akin to a death sentence and that there was a stigma attached to the diagnosis. Many respondents felt strongly about the role of the family in decision making about treatment and care, while others preferred a doctor from the same cultural background who they felt better understood. Other research into the Australian-Italian community found that many respondents believed that cancers with 'roots' were inevitably terminal and also that operating to remove cancer could be a dangerous process.⁹

In Australians with a non-western cultural background, a common theme is the pre-eminence of the family in cancer disclosure and favouring the non-disclosure of a poor prognosis.¹⁰ Cultural beliefs also influenced cancer prevention behaviour, as many Chinese-Australian women had a fatalistic attitude towards cancer and did not perceive cancer prevention strategies as useful, hence were 50% less likely to undergo breast examinations than Australian born women.¹¹ Understanding the culturally influenced behaviours provides useful insight into how this disease is best managed and treated.

The cancer scourge in Indigenous Australians has long been recognised as a blot on the Australian health system and there is acknowledgement that where Indigenous Australians are concerned, "cultural

differences go hand-in-hand with communication barriers."¹² A matched cohort study between Indigenous and non-Indigenous Australians found that "even after adjustment for stage at diagnosis, cancer treatment and greater comorbidity", the Indigenous cancer cases were 30% more likely to die from the diseases than non-indigenous cases.¹³ Low rates of participation, advanced cancer stage at diagnosis and lower surgery rates have consistently shown to be linked to poor cancer outcomes in Indigenous communities.^{5,14,13} Socio-economic disadvantage, racism and geographical remoteness are undeniable contributing factors, yet all researchers, including Indigenous healthcare workers themselves, point to the role that cultural barriers play in the low cancer survival for Indigenous Australians.

Indigenous Australians link cancer causation as a punishment for offending kin members and have strong needs to be close to their land and kin during any cancer care.^{12,15} Consequently, their attitudes towards cancer treatment are shaped accordingly. Many Indigenous women believe that cancer is a fatal disease and yet another ravaging legacy of colonisation.¹⁶ They are also suspicious of treatment strategies because many health workers visiting Indigenous communities are male. Given this context, it is not surprising that they are reluctant to use screening facilities and therefore Indigenous women have higher rates of cancer mortality than non-Indigenous women. Research into the reasons that influence diagnosis, communication, decision-making and treatment of cancer in Indigenous Australians, repeatedly points to the cultural factors in the Indigenous world view such as kinship relationships, religious beliefs, a suspicion of western medication and a slow decision making process.¹⁷

In acknowledging the impact of culture on cancer perception and management, it is vital to remember other factors that influence individual differences in reactions and attitudes to cancer, such as levels of acculturation, age of patient and mixed ethno-cultural legacy. As pointed out by Dein, "it is important to avoid the pitfalls of cultural stereotyping...with those belonging to a specific group holding the same beliefs and behaving in the same way with similar life situations".¹⁸ Nevertheless, what is clear from research into cancer behaviour in numerous countries, is that the core perception of cancer is deeply embedded within cultural contexts and understanding of these contexts is needed to achieve appropriate cancer care strategies.

Emerging strategies to address the cultural aspect of cancer care

The challenge for effective oncology management in diverse populations is to become 'culturally competent'.¹⁹ Yet what exactly does this mean for current health professionals and more importantly, for

future health professionals? In essence it means that health professionals should not pre-suppose that the cancer patient's informational, treatment and emotional needs are congruent with the practitioner's perceptions of appropriate care.

Cultural variations in cancer behaviour indicate that strategies must be customised to suit the cultural norms of patients. For example, the supportive-expressive model of cancer support has been used successfully for many years in the US. This approach consists of semi-structured group meetings of cancer patients and is based on the concept of providing a forum for emotional expression and support networks for cancer patients. This model has proven beneficial in improving cancer pain perception strategies for women with breast cancer²⁰ and also helpful for couples dealing with cancer.¹ Yet the same model of support, applied in different cultural settings such as Hong Kong and France, where the perception and management of cancer is more stigmatised and paternalistic, has been less effective in helping patients to deal better with their cancer. This is because this model, based on open sharing of emotions and cancer perceptions, is not necessarily congruent with the Chinese and French cultural values of disclosure of disease. As demonstrated by the researchers, once the supportive-expressive model is adjusted according to cultural norms, it works effectively to meet the needs of these groups.¹ Hence, cancer support models will only be successful for different cultural groups once they have been adapted to accommodate the differences in culture influenced behaviour of patients.

Cultural factors contributing to low rates of screening and a poorer prognosis include the attitude of cancer fatalism. The perception that cancer cannot be avoided or prevented has been found in studies of groups as diverse as African-American women in the US,²¹ Vietnamese women living in America,²² the Greek community established in Australia²³ and Australian Indigenous women living in remote regions.¹⁶ This belief is directly linked to behaviours such as low uptake of screening programs, late presentation for medical help and rejection of western medication, that lead to a poorer cancer outcome. Educational intervention strategies, which use culturally appropriate lay-persons as informal cancer educators, have shown to be effective in modifying behavioural barriers arising out of cultural beliefs. Where appropriate, the use of spiritual or religious forums of importance to a particular cultural group has also been useful to harness the energy of cultural factors in the fight against cancer. The Witness Program project in the US, which involves African-American cancer survivors publicly demonstrating and discussing their cancer experiences, has addressed the issue of fatalism directly in this cultural group. The implementation of the project has also led to increased

rates of breast cancer screening in African-American women in the US.²⁴

We are one, but we are many

The challenges that face cancer care in multicultural Australia are different from other countries but not unique. Just as health professionals in all countries with mixed cultural heritage have to be aware of culturally influenced cancer behaviour in minority and Indigenous groups, Australian health professionals should also be cognisant of the relevance of the cultural background of their cancer patients.

Becoming culturally competent in the Australian context can be achieved through a multi-pronged approach that adapts successful intervention strategies to our own environment. The positive outcomes of approaches such as supportive/expressive psychotherapy, the Witness Project and the process by which they have been developed need to be recognised and adapted to the Australian environment. This means implementing training strategies for current health professionals and in oncology components of curricula that include:

Recognising the complexity of communication

Language barriers can exacerbate the anxiety of a cancer diagnosis, as can the manner in which cancer disclosure is made. Thus, it is imperative that communication is culturally appropriate with regard to gender and age. For instance, disclosure of cancer to many older migrant Australians should only be made after ascertaining familial preferences. As highlighted by the Australian-Greek community study,²² health professionals should respect the need of certain cultural groups to have family members present with the patient at time of disclosure. Using translators and training more Indigenous health professionals could also be an effective strategy to improve communication channels.

Building useful support networks

It is acknowledged that "despite Australia's multicultural population, there are few groups that offer culturally or linguistically appropriate support to different groups of people affected by cancer".²⁵ Additionally, there are only two support groups for Indigenous Australians and both of these are in urban areas. This highlights the urgent need for the establishment of support groups that address the linguistic and cultural aspects of cancer perception across diverse cultural groups and in the same geographical regions. The Cancer Council's research into support groups suggests that one-to-one peer support services may be more effective than group support. Establishing this type of service for Australians from a non-western cultural background may be a useful strategy in providing cancer support services for such groups.

Understanding and respecting belief systems and developing appropriate methods for behavioural interventions

Health professionals need to acknowledge that for many Australians, cancer and health are simply not just a matter of physical well-being, but are bound up with cyclical notions of life and death. This understanding provides crucial insight into the attitude that certain groups, such as Chinese-Australians and Indigenous Australians, have towards cancer. Research has indicated that despite high levels of acculturation, many Chinese-Australians maintain a traditional view of cancer causation, including factors such as retribution, fate and Karma.²⁶ Being aware of these beliefs and understanding the needs of Chinese patients to access complementary medicine for example, will assist in breaking down some of the cultural barriers towards western cancer care strategies.²⁷ Similarly, understanding Indigenous women's reluctance to access screening programs, due to fears of submitting to foreign and poorly understood treatment options, should provide the impetus for developing other methods.

Adopting an approach that acknowledges the emotional and spiritual aspects of illness and accommodates traditional values, such as receiving treatment from gender specific health providers while remaining in their communities, may also be useful in overcoming the Indigenous communities' resistance to accessing mainstream cancer care services. The success of the American Witness Project indicates that since people are most responsive to information that comes from a role model from the same cultural background, creating a similar initiative that is adapted to suit the cultural beliefs of multicultural communities could be as effective in changing behaviours in the Australian environment.

Understanding of differences in decision making process

Unlike the western concept of personal autonomy and quick action, decision making in many Australian communities including Chinese-Australians and Indigenous Australians is often influenced by kinship groups and collective discussions. Therefore, it is a challenge for health professionals to not enforce decisions or have culturally ineffective timelines. Instead, integrating medical knowledge and experience with community based values by using trained elders

to guide decisions, may foster a greater degree of trust in western health systems and thereby improve cancer outcomes in Indigenous communities.

The Aunty Jean's Good Health Program is an example of a local intervention strategy that incorporates shared cultural values and social connections to engage Indigenous participants in the management of their disease.²⁸ By utilising Indigenous elders as the program's expert reference group, the program has achieved a high level of participation/effectiveness and is an example of how cultural factors can be utilised beneficially. This approach, when applied to cancer care and treatment in Indigenous communities, may be equally successful in providing culturally suitable cancer care behaviours. Programs such as Aunty Jean's have shown a sufficient body of evidence to suggest that interventions which accommodate cultural beliefs, are effective in managing cultural factors hindering the preventive health aspect of diseases.

For emerging strategies to be truly effective in addressing the cancer needs of diverse populations, understanding of and utilising cultural differences is the first crucial step towards improving final outcomes so that culture can be used as leverage and not a barrier in the fight against cancer.

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ACHIEVING COORDINATED CANCER CARE: REPORT ON THE CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA CARE COORDINATION WORKSHOP

Professor Patsy Yates n School of Nursing, Queensland University of Technology

The Clinical Oncological Society of Australia (COSA) has identified cancer care coordination as a priority issue for its members. COSA Council acknowledges the diverse perspectives that exist on cancer care coordination and recognises the value of sharing professional and personal perspectives on care coordination. This paper reports on the outcomes of a cancer care coordination workshop initiated by COSA in November 2006 and provides recommendations for actions which may contribute to improved cancer care coordination.

Need for coordinated cancer care

Cancer treatment and follow-up care for many people is complex and multifaceted. Patients and their families report becoming 'lost' in the system, with numerous reports that many patients continue to experience unnecessary morbidity and distress.¹

Screening, diagnosis, treatment and supportive care for patients with cancer are typically provided by different services and providers, often with limited coordination, leading to fragmented care, sub-optimal management and high healthcare costs.^{2,3} The fragmentation of care is exacerbated by the absence of clear referral pathways and sub-optimal communication between healthcare providers and between providers and patients. These features of our cancer care system mean that:

- n many patients experience confusion and lack of information during their encounter with cancer care services delivered by multiple carers and often in multiple sites;
- n many patients experience lack of adequate support and unmet information needs;
- n many patients do not access appropriate care;
- n there is an acute lack of support for rural patients with cancer and for some patients treated outside specialist centres.⁴

The need to address fragmentation, or the lack of continuity of care, has been highlighted by many people

with cancer in Australia and in several national reports. The *Optimising Cancer Care in Australia* report identified the lack of an integrated care system for people with cancer as a key priority for health care reform.¹ The National Service Improvement Framework for Cancer acknowledges that a more coordinated approach to cancer care in Australia is required to improve treatment and support for people with cancer.⁵ The report identifies an optimal service as one in which people with cancer "will experience the cancer journey as seamless and continuous care provided by one integrated service". It notes that achieving such continuity of care requires linkages and coordination:

- n among different treatment modalities;
- n among various health professionals and care providers;
- n among different individuals within the same discipline (eg. medical or nursing staff on rosters);
- n within any single service, over time;
- n across the spectrum of cancer care (from detection through treatment to palliative care); and
- n across different service types and settings (public and private, inpatient and ambulant, general and specialist hospitals).⁵

Delivering care in an integrated and coordinated manner is likely not only to enhance the patient's experience and minimise the likelihood of further distress, but also contribute to improved clinical outcomes and efficiency in delivering health care services.

Forum for exploring strategies

A one-day workshop was convened, prior to COSA's 2006 Annual Scientific Meeting in Melbourne, to provide a forum to explore strategies for achieving improved care coordination, reviewing progress in this area to date and identifying possible future directions. The program was developed by a working group comprising representatives

of state government departments, organisations with experience in developing care coordination strategies and the sponsoring organisations.

Objectives for the workshop were to:

- n define the problems of care co-ordination;
- n provide some context for exploring a range of strategies for achieving care coordination, at the system, organisational, team and individual level, including the role of care coordinators; and
- n review evidence and experiences with care coordinators, from the perspective of consumers, care coordinators, health care teams and policy makers.

It was recognised that an important outcome of the workshop would be identification of issues and areas for future development in care coordination in metropolitan, regional and rural settings.

A total of 46 invited participants attended the workshop. Participants included key stakeholders with responsibility, experience and expertise in care co-ordination at the national, state/territory and local levels. COSA distributed a comprehensive discussion paper prior to the workshop, summarising the literature on care coordination and outlining care coordination initiatives being implemented at national and state levels. The program and discussion paper are available at www.cosa.org.au.

Summary of discussions

Context for discussion

A series of presentations set the context from consumer, system and evidence perspectives. In opening the workshop, Professor David Currow, CEO of Cancer Australia, noted that it was important to ensure that discussions about care coordination be centred around the person with cancer, rather than being provider focused.

Dr Ian Roos shared a number of examples of gaps and problems that he and fellow consumers of cancer services had experienced due to a lack of care coordination. Dr Roos' key messages centred around the importance of care coordination from the consumer's perspective, such as improved access to medical records, sharing of information between health professionals, health care settings and patients. He emphasised the importance of systems re-design to achieve care coordination and highlighted the risks associated with investing coordination responsibilities with one person.

Professor Patsy Yates provided a review of the literature which emphasised identification of strategies for achieving care coordination at the systems, organisational, team and individual levels. Professor Yates also reviewed recent studies on case management which had reported improvements in continuity of care and a range of other clinical and psychosocial outcomes. Models tested involved highly specialised roles and intensive interventions, however the effectiveness of such approaches in day-to-day clinical practice had not been tested.

National, state/territory and local initiatives

Key issues, challenges and learnings from initiatives at the national, state/territory and local levels were explored, with presenters highlighting a variety of approaches to improving care co-ordination taken by jurisdictions and individual organisations. These included improving communication and coordination within multidisciplinary teams, restructuring cancer services to achieve more integrated systems, promoting local collaboratives and clinical networks, defining patient management frameworks and protocols, and appointing cancer care coordinators.

Key learnings included the importance of building relationships, flexibility in the use and application of models, use of a variety of strategies and ensuring that coordination was seen as a responsibility of all members of the health care team. Panel members and presenters also emphasised that direct benefits and outcomes of care co-ordination strategies would need to be demonstrated through a variety of measures, which may include patient views of their experience, team views of their functioning, measurable improvements in service delivery, evidence of coordination within and across the system, and evidence of continuity of care. Importantly, the increasing emphasis being placed on care coordination strategies at all levels was seen to have been a catalyst in changing practitioner views and mindsets about multidisciplinary care teams, encouraging practitioners to think outside their traditional role boundaries and ways of practice.

These sessions highlighted that care coordination was not a single solution or one that could be pursued in isolation of broader system solutions, and that sufficient focus needed to be placed on change management issues, particularly engaging with practitioners in both the tertiary and primary care settings and building relationships. Efforts to achieve care co-ordination also brought professional roles and role boundaries into sharper focus, requiring that the implementation of care coordination improvements needed to be supported by clear role definition.

Current challenges and opportunities in improving cancer care coordination

Workshop participants were invited to identify issues and challenges in achieving improved care coordination. Table 1 provides a summary of the major issues, gaps and opportunities highlighted by participants.

An important outcome from the workshop was the identification of a set of principles for care coordination that may be used to guide future initiatives. These principles are presented in Table 2.

Future directions

The importance of identifying further professional development opportunities was highlighted by the workshop. Participants also recommended that project teams responsible for the EdCaN and Cancer Professionals Continuing Professional Development projects, currently funded through the Australian Government's Strengthening Cancer Care Initiative, should pay particular attention to care coordination issues in developing their programs.

Table 1: Issues, gaps and opportunities in improving cancer care coordination

Issues and gaps

- n The consumer's perspective of lack of care coordination is reflected in a range of experiences, and includes:
 - n inadequate information exchange between health care providers and patients, between health care providers themselves, and between various sectors of the health care system;
 - n gaps and delays in access to services that are appropriate to individual needs;
 - n inefficiencies in service delivery.
- n Importance of learning from care coordination initiatives and programs already underway at national and jurisdictional level.
- n Need for system level changes to ensure care is coordinated.
- n The fact that many care coordination strategies currently take a provider focus rather than a consumer focus.
- n Limited integration of primary care providers in care coordination activities.
- n Better understanding of the benefits to be achieved, and the risks associated with care coordination roles.
- n Need to support all health professionals to contribute to care coordination.
- n Specific support needs for health professionals appointed to dedicated care coordination roles, and the importance of integrating these roles within the team and broader system-level strategies for achieving care coordination.

Opportunities

- n Address funding and resourcing issues, including:
 - n development and utilisation of new funding models, including optimising the use of MBS items to support care co-ordination;
 - n impact of financial implication on patient decisions.
- n Build patient empowerment through:
 - n patient-held records or electronic records, including patient care pathways;
 - n improved communication;
 - n support with transition;
 - n support with self-management of co-ordination;
 - n provision of service directories.
- n Improve communication with primary care providers by:
 - n improved access to information including treatment plans;
 - n increased use of discharge planning;
 - n addressing barriers resulting from professional boundaries between GPs and other specialists (for example by enabling GPs to deliver chemotherapy);
 - n better utilisation of practice nurses.
- n Build sustainability in care co-ordination, through:
 - n workforce and career development and succession planning;
 - n professional development;
 - n management support;
 - n mentoring and coaching;
 - n clinical supervision.
- n Standardise care by:
 - n defining outcomes, standards and indicators;
 - n improved clarity around role definition;
 - n using structured referral pathways;
 - n measuring achievement against milestones.
- n Address rural and remote issues.

Table 2: Principles for care coordination

<p>Patient focus</p> <p>Care coordination should:</p> <ul style="list-style-type: none"> n be patient, carer and family-centred; n be a key focus across the entire cancer journey; n enable patient choice (to not receive care coordination); n emphasise patient empowerment; n improve patient access to services; n address equity of access; n improve care outcomes. <p>Team focus</p> <p>Care coordination takes a multidisciplinary team approach and is inclusive of medical and allied health professions in both tertiary and primary settings, as well as management and administrative staff. Care coordination:</p> <ul style="list-style-type: none"> n focuses across the continuum of care; n is a shared responsibility, and is not solely the responsibility of an individual coordinator; n relies on the sharing of information and knowledge. <p>Systematic approach</p> <p>Care coordination should:</p> <ul style="list-style-type: none"> n be evidence-based; n be sustainable and supported; n take a system-based approach; n be capable of use across different platforms, including public and private systems, metropolitan and rural and remote geographical settings and various care settings; n be built on a sound and robust evaluation framework.
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Research was also needed to ensure an evidence base for cancer care coordination. As a starting point, it was recommended that a scoping study of professionals with care coordination responsibilities be undertaken to better understand practices and professional development needs.

COSA Council is encouraging ongoing discussions among those working in care coordination roles, to build on the outcomes of this initial meeting. A second workshop, focused primarily on developing consensus around issues such as role definition and scope of practice, competency standards/performance indicators for care coordinators and professional development and support requirements, is now being planned.

Acknowledgements

COSA gratefully acknowledges the financial support for the workshop from Cancer Australia and the Cancer Institute NSW. COSA also acknowledges the assistance of: members of COSA Council and staff; the Care Coordination Working Party who organised the workshop program; Lisa-Maree Herron for preparing the workshop discussion paper, parts of which have been included in this report; and Mr Doug Smith from Palm Consulting Group who facilitated the workshop and prepared the

summary report on care coordination principles. The contribution of participants to the workshop discussion is much appreciated.

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AUSTRALIAN BEHAVIOURAL RESEARCH IN CANCER

Cancer Prevention Research Centre, Queensland

Exercise for health: a breast cancer recovery project

Breast cancer is the most common type of cancer experienced by Australian women. Although the incidence is high, so too is the chance of survival, with the five-year relative survival rate now greater than 85%. Thus, there is an increasing interest in interventions to improve the quality of long-term survival.

There is an accumulating body of evidence supporting the role of exercise in reducing symptoms and improving both the quality and quantity of survival among women following breast cancer. However, most studies have been conducted overseas and with women in urban areas. There is therefore a need to develop and evaluate exercise rehabilitation programs that are feasible to deliver to Australian women living outside of metropolitan areas.

The current pilot study, funded by the National Breast Cancer Foundation, is a collaboration between The University of Queensland Cancer Prevention Research Centre and Queensland University of Technology Institute for Health and Biomedical Innovation. It is a randomised, controlled trial of an eight month, telephone delivered exercise rehabilitation program designed to reduce physical symptoms and improve quality of life among women undergoing breast cancer treatment in rural, regional and remote areas of Queensland. This study forms an arm of a larger study that is currently being undertaken at Queensland University of Technology with an urban sample of women who have received breast cancer treatment via Brisbane based hospitals.

Recruitment for the rural arm began in April 2007, with eight regional Queensland hospitals and six breast care nurses involved in the study. Sixty women have been enrolled to date, with the goal of recruiting 140 women.

Centre for Cancer Control Research (CCCR) and Behavioural Research Evaluation Unit (BREU), South Australia

Progress in tobacco control: results from the 2006 Health Omnibus Survey

The Health Omnibus Survey is a state-wide annual survey of 3000+ respondents. The results revealed that smoking prevalence for the population overall did not change significantly from 2005 to 2006. Most smokers made a quit attempt at some point and approximately

one third of smokers made a quit attempt in the past year.

Evaluation of SmokeCheck Tobacco Brief Intervention training course (TCRE)

SmokeCheck training aims to enable health professionals working with Indigenous clients to raise awareness of the risks of tobacco use, help clients determine their readiness to quit and support those interested in quitting. Results indicate that participants were satisfied with the training, which was effective in improving knowledge regarding health effects of smoking. TCRE is currently following-up with clients who have received tobacco brief interventions by trained health professionals.

Smoke-Free Pregnancy Project: 24 month case note audit (CCCR)

In 2004 a hospital based project that targeted pregnant smokers and their partners was introduced into multiple South Australian hospitals. The main component of this program was to train antenatal staff to run a brief intervention with pregnant patients. The 24 month case note audit involved analysing the smoke-free assessment and intervention form of all patients presenting for their first antenatal visit within a selected three month period in early 2006. Results suggested that the project has been implemented successfully in all hospitals.

Evaluation of the smoke-free cars legislation in South Australia (TCRE)

TCRE will be conducting focus group testing in August to assess parents' opinions of legislation banning smoking in cars when children under 16 years are present. Results will be available in late 2007.

Cancer Information Centre pilot project (CCCR)

In August 2006, a Cancer Information Centre (CIC) was launched at the Royal Adelaide Hospital. The aim of this project was to give information and support to cancer patients undergoing radiotherapy and their families through providing paper resources, electronic access to resources and a direct line to The Cancer Council Helpline onsite in the radiotherapy department. Evaluation of the CIC is currently underway, using staff surveys, surveys of consumers and semi-structured interviews with volunteers.

Viertel Centre for Research in Cancer Control (VCRCC), Queensland

'CanChange': a psychological and lifestyle support program for colorectal cancer (CRC) survivors

Colorectal cancer is the most common cancer that

affects both men and women in Australia. As our population continues to age, there will be an increasing number of people diagnosed with colorectal cancer, which will create a higher demand for cancer services. The diagnosis and treatment of colorectal cancer is a major life stressor that is followed by a range of psychological, social and physical difficulties. Over time, most people diagnosed with CRC go on to adjust to their changed life circumstances without clinical intervention; however 30-45% of people report ongoing, clinically significant distress. Distress in cancer patients is also directly associated with poor health outcomes and poor lifestyle behaviours, including daily cigarette smoking, physical inactivity and obesity. However, cancer survivors who adopt positive lifestyle behaviours can enhance their quality of life, reduce the risk of cancer recurrence and development of other chronic diseases and extend survival.

CanChange is a telephone delivered psychological and lifestyle support program to address the unmet supportive care and lifestyle needs of colorectal cancer survivors. CanChange is currently being developed and piloted, with plans to conduct a full randomised control trial. The program has been developed in consultation with colorectal cancer survivors and health professionals and is a collaborative project with the University of Alberta (Canada), University of Queensland and The Cancer Council Victoria. It is expected that participants exposed to the program will have improved quality of life, decreased psychological distress and the necessary skills to adopt and maintain a healthy lifestyle.

Sexual functioning after radical prostatectomy

Prostate cancer is the most common male cancer in the Western world. The most substantial long-term morbidity from this cancer is sexual dysfunction, with consequent adverse changes in couple and intimate relationships. Research to date has not identified an effective way to improve sexual and psychosocial adjustment for both men with prostate cancer and their partners. As well, the efficacy and cost effectiveness of peer counselling as opposed to professional models of service delivery has not yet been empirically tested.

Normalising help seeking for sexual problems; setting realistic goals and expectations about sexual function after treatment; reinforcing the need for flexibility, patience and persistence in managing erectile dysfunction; and encouraging and teaching a problem solving approach may be helpful in sexual rehabilitation. A further approach is the integration of elements of sex therapy, such as sexual communication and stimulation, with medical treatments for erectile dysfunction. A recent pilot of a four session counselling program to enhance sexual rehabilitation after treatment for localised prostate cancer produced improved sexual satisfaction in both men and their partners at three month follow-up, and increased utilisation of medical treatments for erectile dysfunction at three and six

months. The author of the intervention (Schover, MD Andersen Cancer Centre, Houston) has since developed a CD-Rom version of the program and has agreed to partner with The Cancer Council Queensland in research to assess the efficacy of this approach if paired with professional advice from a prostate cancer nurse counsellor compared to peer support.

Centre for Behavioural Research in Cancer (CBRC), Victoria

Potential for smoke-free policies in social venues to prevent smoking uptake and reduce relapse: a qualitative study

The purpose of this study is to understand the utility of smoking in pubs/bars and nightclubs and explore perceptions of how smoke-free policies might influence smoking behaviour. Qualitative focus group methodology was used involving young social smokers and older regular smokers. Pubs/bars and nightclubs were valued as the few remaining indoor public places where people could relax and smoke. These venues were perceived as encouraging smoking and facilitating smoking relapse. For young social smokers, smoking provided an opportunity to be part of a "cool" in-group. Older regular smokers felt pubs/bars provided strong cues for smoking relapse. Smokers felt they would adapt to smoke-free policies and expected these policies to reduce their smoking or assist quitting. Smoke-free policies in pubs/bars and nightclubs may assist smokers to quit and make it less likely that young social smokers will progress to regular smoking.

Wakefield M, Cameron M, Murphy M, Health Promotion Practice (in Press)

Portrayal of tanning, clothing fashion and shade use in Australian women's magazines, 1987-2005

This study aimed to examine whether the portrayal of tanning and clothing fashion for spring and summer in popular Australian women's magazines over the past two decades has been consonant or dissonant with skin cancer prevention objectives. Nearly 5000 full-colour images of Caucasian females were coded for depth of tan, extent of clothing cover, use of shade and setting. Most models portrayed outdoors did not wear hats and were not in the shade. Between 1987 and 2005, the proportion of models depicted wearing hats decreased and the proportion of models portrayed with moderate to dark tans declined then later increased. Younger women were more likely to be portrayed with a darker tan and more of their body exposed. Models with more susceptible phenotypes (paler hair and eye colour) were less likely to be depicted with a darker tan. Darker tans and poor sun protective behaviour were most common among models depicted at beaches/pools. It was concluded that implicit messages about sun protection in popular Australian women's magazines contradict public health messages concerning skin

cancer prevention.

Dixon H, Dobbinson S, Wakefield M, Jansen K, McLeod K. Health Education Research (in press)

How does a cancer education program impact on people with cancer and their family and friends?

This study reports on the effects of patient education (ie. the Living with Cancer Education Program) for people with cancer in comparison to family and friends. Data for this report are from 666 participants with cancer and 324 family and friends who completed pre and post-program questionnaires. The majority of participants were female and self-reported a broad range of cancer types. Results showed high levels of participant satisfaction with the program and positive changes in measures such as illness perceptions and emotional functioning. In many cases, the pattern of change was different for people with cancer compared to family and friends. For example, family and friends felt more worried and stressed than people with cancer at entry into the program. Although these feelings decreased for both groups, the change was greater among family and friends. These findings suggest this education program may be useful for helping people with cancer cope with the disease, with some distinct benefits for family and friends.

Sutherland G, Hoey L, White V, Jefford M, Hegarty S. Journal of Cancer Education (in press)

Centre for Health Research and Psycho-oncology (CHeRP), NSW

Development of a consumer toolkit to facilitate needs based access to palliative and supportive care services

People with advanced cancer, their caregivers and families experience high levels of physical, psychological, social and spiritual needs. Although people consistently report improved well-being and outcomes in these areas with access to specialist palliative care services, referral in Australia often occurs too late for needs to be properly addressed or when the patient and/or family is experiencing crisis. The objective of the proposed project is to develop a consumer initiated strategy to facilitate needs based access to palliative care services for people with advanced cancer and their families.

CHeRP, in conjunction with The Cancer Council NSW, will develop a consumer toolkit, including information about palliative care for people with a life-limiting illness and their caregivers. It will also include a self-assessment tool for patients and their caregivers to identify their levels of unmet psychological, social, physical and spiritual needs, their need for additional support, and to communicate these to their healthcare team. After extensive consultation with consumers and health professionals, the draft toolkit will be evaluated to measure its usefulness in reducing levels of unmet need and increasing appropriate access to specialist

palliative care services.

This project will extend the national seven-year program of research into needs based palliative care. The consumer toolkit will complement the already developed Palliative Care Needs Assessment Guidelines and Palliative Care Needs Assessment Tool for use by health professionals.

A qualitative study of recent cancer survivors' needs

It is well documented that people diagnosed with cancer report unmet needs across a range of domains, with the highest levels usually being psychological, physical aspects of daily living and sexuality. The objective of this research was to gain a deeper understanding of the needs of diagnosed cancer patients, including the strategies they use to manage their needs and the support they would find beneficial. A total of 10 women and 12 men from NSW and Victoria, diagnosed with cancer six to 12 months ago, took part in a semi-structured telephone interview.

Most survivors described how inadequately prepared they were for the treatment they received and the impact of cancer on their life, with the side-effects of treatment often more severe than they had expected. These survivors would have preferred a 'warts and all' appraisal of what to expect both physically and emotionally.

Overwhelmingly, survivors credited the emotional support received from family and friends as being the most important factor contributing to how they coped with their illness, but were concerned about the burden that this placed on family members. Many found it difficult to find out about support available at each stage of their illness and thought it would have been valuable to talk to someone who had been through a similar cancer experience.

Many survivors relied on the practical support and assistance of family and friends and this was often associated with feelings of guilt. They felt that financial assistance should be made available for practical help around the house. Those who travelled long distances for treatment reported this to be a large burden physically and financially and transport and accommodation assistance schemes were perceived as complicated and slow.

Centre for Behavioural Research in Cancer Control (CBRCC)

A home-based physical activity and nutrition (PAN) program for seniors

Regular physical activity and a good diet are important protective behaviours against a number of cancers. CBRCC evaluated the effectiveness of a three-month home-based physical activity and nutrition (PAN) intervention for 65-74 year-old adults residing in Perth. Of the 248 seniors recruited, 114 (46%) were randomly selected

for the PAN program with the remaining participants serving as the control group. A booklet containing information on dietary guidelines, recommended physical activity levels and suggestions on how to set goals to improve diet and physical activity was delivered to the intervention group by mail. A questionnaire was posted to all participants pre and post-intervention. Compared to controls, the intervention group demonstrated a significant increase in fibre intake ($p < 0.01$), but not fat-reduction dieting ($p > 0.05$), after adjusting for body mass index and other demographic confounding variables. Post-intervention walking showed an average gain of 27 minutes per week for the PAN participants in contrast to a five-minute drop for the controls ($p < 0.01$). The results suggested participants became more aware of their health and well-being after the program, which was successful in improving fibre-intake and walking for recreation among seniors.

Automating the association between the terms 'smoking' and 'disgusting'

When most Australians are asked "Which bank?" their automatic conditioned response is "Commonwealth Bank", thanks to a successful advertising technique employed by the organisation. It is our aim to see a similar conditioned response among young West

Australians formed between the terms 'smoking' and 'disgusting'. Formative research was undertaken with Perth students aged 14 to 16 years to create a list of concepts they find most disgusting. These have been used to develop a series of rough-cut television advertisements linking smoking to other disgusting concepts, including excrement, fetid garbage, cockroaches and maggots. The advertisements have been evaluated with adolescents using the ad test technique, via intercept interviews, and have performed just as well, and in many cases better, than existing youth tobacco control advertisements. We are now investigating whether the concepts described above will be equally effective with young adults. To this end we are surveying 200 young adults aged 18 to 24 years. The results will allow us to determine whether 'disgusting' concepts dreamt up by 14 to 16 year-olds hold similar resonance with 18 to 24 year-olds and whether the present suite of ads are likely to work with this older age group. If there is disparity between the two age groups, the research will inform concepts for future ads that are more likely to appeal to 18 to 24 year-olds. The eventual aim is to have advertisement end-frames simply reading "Smoking is..." requiring psychological participation by viewers to answer "disgusting".



Cancer Council applauds Prime Minister's call for solarium regulation

The Cancer Council Australia welcomed Prime Minister John Howard's announcement that he would ask Health Minister Tony Abbott to look at uniform national laws on solarium use in Australia.

Chief Executive Officer, Professor Ian Olver, said solarium use significantly increased the risk of skin cancer and that the proliferation of solariums across Australia without any reasonable safety controls was a serious public health issue.

Professor Olver said recent research showed that the number of solariums in Australian capital cities had increased fourfold over the past decade, with more than 400 solariums operating without any uniform regulation to help reduce their potential for skin cancer death and disease.

He said research also showed that the current

voluntary code was not working, with evidence of poor industry compliance in areas such as restricting solarium use for people aged under 18 and little understanding of the serious health risks posed by solarium use.

"In a nation that has for many years had the world's highest skin cancer incidence and mortality rates, it is unacceptable that we significantly increase our risk of a potentially deadly disease through artificial means in an unregulated environment," Professor Olver said.

"Solariums can produce UV radiation up to five times stronger than the midday summer sun and, when used before the age of 35, increase melanoma risk by up to 75 per cent."

Cancer Council website receives a face-lift



Following extensive internal and external review, The Cancer Council Australia has launched its revamped and updated website.

Boasting a fresh and vibrant new look, the site overhaul includes a more prominent health professionals section and improved navigation to ensure visitors can more easily and quickly find the information they need.

A new section on Cancer Types has been added and will be developed further in the coming months. Other developments in the pipeline include a micro-site for The Cancer Council's journal, Cancer Forum.

Visit www.cancer.org.au for up-to-date cancer information for both health professionals and consumers.

Urgent action needed to improve cancer programs and services for regional Australians

A report showing regional Australians have higher rates of cancer incidence and mortality than city dwellers emphasised the need for increased investment in cancer prevention and a national approach to improving services such as patient travel and accommodation schemes, according to The Cancer Council Australia.

Commenting on the Australian Institute of Health and Welfare report, Cancer in Australia: an overview 2006, The Cancer Council Australia's Chief Executive Officer, Professor Ian Olver, said the report confirmed all-cancer incidence and mortality were higher for Australians in rural and regional areas.

Professor Olver said he was concerned about higher rates of cervical cancer, melanoma and smoking related cancers in regional areas. "We need to invest more in promoting the importance of regular Pap tests, ensure Indigenous girls in remote communities are receiving the HPV vaccine and educate Australians generally about the risks associated with sun exposure and smoking. Reinvigorating the National Tobacco Strategy, which includes measures to reduce smoking prevalence in regional areas, is one way governments can work

together to help smokers quit.”

Cancer Council, COSA call for overhaul of patient travel assistance schemes

A whole-of-government commitment to boosting the funding and efficiency of patient travel and accommodation assistance schemes is needed to help reduce geographical inequities in cancer care outcomes, Australia's peak non-government cancer control organisations said.

Responding to an ongoing Senate inquiry, the Chief Executive Officer of The Cancer Council Australia, Professor Ian Olver, and the President of the Clinical Oncological Society of Australia (COSA), Professor David Goldstein, said patients in remote areas were not accessing treatment they needed because of under-funded, fragmented travel and accommodation assistance.

They said national leadership and a shared commitment across jurisdictions was the best way to bring patient travel and accommodation schemes into line with need.

The Cancer Council Australia/COSA submission to the Senate inquiry is available at: <http://www.aph.gov.au/>

Pink Ribbon Day

Women across Australia purchased ribbons, wristbands and t-shirts from The Cancer Council's range of Pink Ribbon Day merchandise during October to show their support for the 1 in 9 women who will be diagnosed with breast cancer.

The funds raised will help The Cancer Council to fund breast cancer research and provide support to



'Girls just wanna have fun'

More than 15,000 Australian women are diagnosed with breast, cervical, ovarian, vaginal or uterine cancer each year.

In October, thousands of women across Australia got together for a 'Girls Night In' to raise funds for women's cancers.

Girls Night In is a unique event that brings friends, workmates and family together for an evening of fun and entertainment at home. Participants donate an equivalent amount of money to what they would have spent



Alcohol, Tobacco and Cancer

Editors C.H. Cho & V Purohit

Karger, 2006

ISBN: 3-8055-8107-6

312 pages

RRP: \$US207.25

Alcohol and tobacco consumption are strongly linked with many cancers. Cho and Purohit have provided a clear overview on the mechanisms by which cancer develops at a number of sites in the body.

The book begins with a sound summary of the mechanisms of cancer and presents the latest evidence associated with host susceptibility, environmental, infection and dietary factors.

Experts in their related fields of research outline the many intrinsic ways high alcohol consumption damages cellular pathways. The digestive tract, stomach, large intestine, liver, pancreas and breast are covered in considerable depth and dedicate specific information on the carcinogenicity associated with each organ.

The second part of the book is committed to tobacco and its effect on the formation of cancers of the lung and digestive tract. There is a comprehensive chapter on the actions of nicotine in the development of cancer.

The final chapters review the role of phytochemicals and vaccines. Lifestyle dietary changes as a chemopreventive purpose tend to hold strong interest with both health professionals and the general population. Although there has been a great deal learnt about the inhibitory activity of cruciferous isothiocyanates and tea flavinoids in the laboratory setting, chemoprevention activity in lung cancer in particular needs more detailed mechanism-based trials.

As a succinct scientific overview of the underlying mechanisms which initiate or promote carcinogenesis this book is a valuable resource. It also furnishes the latest research on chemopreventive agents and nicotine vaccine and their possible approaches to reducing lung

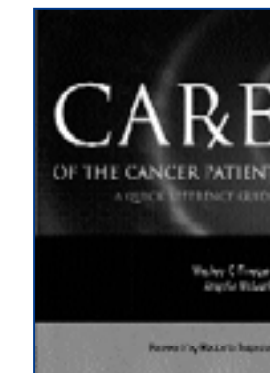
cancer.

Kathy Ansell,

Cancer Information and Support Services,

The Cancer Council NSW, Sydney NSW

Care of the Cancer Patient: a quick reference guide



Wesley C Finegan, Angela

McGurk

Radcliffe Publishing (2007)

ISBN-13: 978-1-84619-128-2

312 pages

RRP: \$59.95

What a find! Care of the Cancer Patient is what I consider a must have for every library

on oncology/palliative care wards. Intended for the non-specialist nurse, it is a fantastic resource for the novice, junior or student nurse.

The information in this text book covers everything from A-Z when caring for the cancer patient. The authors use the acronym CARE when creating management plans for the nursing cancer patients:

C – Consider all of the patient's symptoms

A – Assess the signs and symptoms

R – Remedy for the problem is appropriate

E – Extra information

CARE has been tailored so that it can be adapted for most situations, in order to promote the best outcomes in cancer nursing. I found this system very

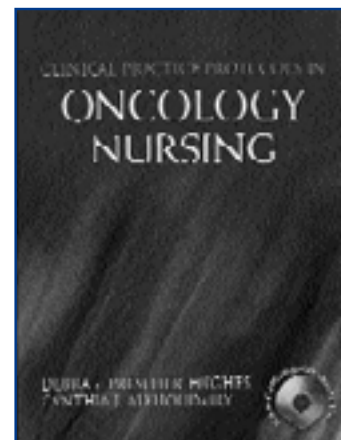
straight-forward to follow. There are valid examples of CARE management plans in this book such as the management of terminal restlessness for a new graduate palliative care nurse. The CARE principle encourages nursing staff to explore why the patient may be agitated or anxious and provides solutions, both non-pharmacological and pharmacological.

The book is set out in a very easy-to-use manner and the information and vocabulary is simple to understand and follow.

In 2004, the UK National Institute for Clinical Excellence published a paper called Guidance on Cancer Services, which aims to improve supportive and palliative care in adults with cancer. Care of the Cancer Patient helps guide the nursing staff in the cancer care setting so that the best evidence-based practice is achieved.

Since reading this book I have recommended it to nursing colleagues in educator and management roles within oncology/palliative care wards. Not only is it a great basic reference guide to have on wards, but it is also very affordable.

Tracy Cosgrove,
Royal North Shore Hospital, Sydney, NSW.



Clinical Practice Protocols in Oncology Nursing

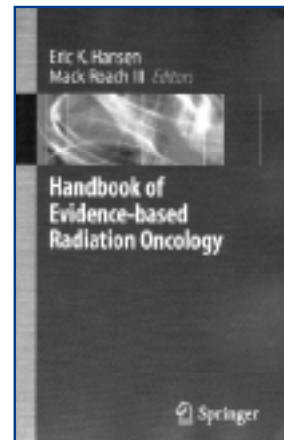
D.S. Prescher-Hughes, C.J. Alkhoudairy
Jones and Bartlett, 2006
ISBN: 978-0-7637-3639-2
675 pages
RRP: \$73.00

This book is an excellent resource, not just for oncology nurses but for pharmacists and doctors alike. It provides a quick and easy reference to current treatment protocols for many cancers. This is not just a book full of chemotherapy protocols, but also includes chemotherapy/radiotherapy regimes. The author states in the preface that "Clinical Practice Protocols for Oncology Nursing has been a work in progress for 20 years". From reading through the book I can certainly see why.

Each protocol contains 11 different categories or 'recipes' for administration, including agents involved, baseline laboratory tests required prior to administration, premedications needed, initiate IV (for the intravenous solution required if specific), administration information for each drug in the regime, major side-effects, supportive drugs, antiemetic protocol post chemotherapy, treatment schedule, and the estimated number of visits. Finally, each protocol includes a patient details section for height/weight and BSA, along with patient name, ID number and diagnosis. There are also physician details and signatures for those responsible for calculating the dosage. As most medical protocols only contain the drugs and administration schedule, the additional information like major side-effects and antiemetics post-completion is more pertinent to nursing staff who administer these medications.

The treatment schedule information is a bonus for unit managers and day care units, as they plan follow-up appointments and subsequent treatments, making scheduling a much easier process.

Finally, in a time where most of our work is computerised,



the book comes equipped with a CD-ROM, enabling the downloading of all the protocols found in the book on to department PCs. The CD-ROM allows changes to be made that are relevant to individual departmental policies and procedures for IV fluids, fluid volumes, antiemetics and other supportive medications. Individual protocols can then be printed for each patient to store in their treatment record for future reference.

The one thing I feel is missing from these protocols is a section for the names and signatures of those administering the medications. If these were included it would allow departments to utilise these protocols as pre-printed chemotherapy charts.

Despite this, we are currently looking at installing the CD-ROM on to our nursing computers to enable nurses to have access to this vital information. This book is a great reference to anyone involved in the administration of sometimes complex chemotherapy/radiotherapy regimes.

Megan Hayes,
Oncology Unit, Austin Hospital, Melbourne, Victoria.

Handbook of Evidence-based Radiation Oncology

E.K. Hansen, M. Roach III (Eds)
Springer (2007)
ISBN: 0-387-30647-1
536 pages

This handbook was compiled by members of the Department of Radiation Oncology at the University of California, San Francisco, and represents evidence-based radiation oncology treatment protocols used at that institution.

The first impression is of an attempt to cram too much data into 500 odd pages, perhaps inevitable in a publication aiming to be comprehensive enough to cover the field, but concise enough to be a vademecum. The smooth flow of the text is lost to the type of shorthand reminiscent of individual study notes, and a no holds barred approach to abbreviations. Many, but by no means all of the abbreviations are explained in a list concealed towards the back of the book. The explanation of several would be unexpected to many. SCV, for example, means supraclavicular in this text

rather than subclavian vein. Others are frankly tortured attempts at brevity such as 'qAM' for every morning.

Nevertheless, despite an initial struggle for the reader to come to terms with this high level "data compression", the 40 subject chapters do indeed comprehensively cover the use of radiation oncology for cancer. The chapters are presented in a standardised format starting with a section quaintly named 'Pearls'. This standardised format for each type of malignancy would be familiar to many involved in preparing institutional treatment guidelines. Reference to the pertinent recent medical literature and major clinical trials is admirably thorough, although not surprisingly slanted towards North American studies. Australian readers will be pleased to note the reference to the Trans-Tasman Radiation Oncology Group trial 96.01 in the chapter on prostate cancer. On the other hand, they will also note that the chapter on skin cancer, including melanoma, refers almost exclusively to US sources without mention of Australian studies on this particularly Australian class of malignancy.

The need for economy of words usually means final treatment recommendations are made without discussion of options suggested by the trial evidence cited. For example, for early stage testicular seminoma, the chapter refers to the 2005 MRC trial report indicating that prophylactic para-aortic irradiation of 20 Gy in 10 fractions gives similar disease control to 30 Gy, with less short-term morbidity. Despite this, the book recommends without further explanation a dose/fractionation prescription of 25.5 Gy in 17 fractions.

Apart from such reservations, this handbook is brimming with information and recommendations relevant to the day-to-day practice of radiation oncology. Who would find it useful in Australia? The information is too concentrated and specialised to be of practical use to general practitioners, residents passing through radiation oncology or to most radiation oncology nursing or therapy staff. For radiation oncology registrars, it would serve as a useful potted summary of much of their reading for the Part II exam, and for signposting significant journal articles and trial reports for further reading. For the radiation oncologist? Ideally, radiation oncology centres should be structured so that subspecialty groups prepare their own evidence-based and referenced guidelines (or embrace national ones), with their own internet-based literature searches for evolving or unresolved issues.

In reality of course, this often remains no more than an ideal because, for example, of the daunting need for busy radiation oncologists in smaller centres or outreach clinics to maintain a working knowledge of all cancer types. For many Australian radiation oncologists, this book would thus be a helpful concise reference to keep at hand.

Guy Bryant,
Southern Area Radiation Oncology Services,
Mater Centre, South Brisbane, Queensland.

Life, Happiness & Cancer – Survive with Action and Attitude!

Phil Kerslake
Steele Roberts Publishers(2006)
ISBN 1-877338-87-7
176 pages
RRP: \$29.99

In 1979, Phil Kerslake was 19 years old when diagnosed with non-Hodgkin's lymphoma. Almost 30 years and many treatments, relapses and recoveries later, leading to personal enquiry, experience and experimentation, he is able to provide guidance to other people with cancer on the strategies and life changes that he believes were key contributors to his ability to tolerate and survive these challenges.

Nowadays, when there are hundreds of self-help books on the market for cancer patients, it is enlightening to find one that provides no nonsense, easy-to-comprehend and achievable strategies and approaches that are flexible and able to be individualised. This book can encourage and facilitate the drive that individuals require to take back some control at all stages of the cancer trajectory.

This is not a book to be read once and then placed on the shelf. Rather, it should be used as a guide book that is referred to on a daily basis with the intended outcomes of:



- n Enhancing a person's ability to cope physically, mentally and emotionally.
- n Achieving optimum

- effects from primary treatment regimes.
- n Stimulating the body's natural healing mechanisms and resistance to cancer.
- n Development of a positive point of view to enhance quality of life during and after cancer.

Kerslake stresses that while reading the book passively can provide some benefits, it will be the active integration of some or all of the tools that will yield the most significant results.

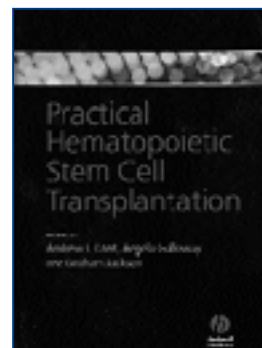
Life, Happiness & Cancer is targeted at cancer patients, relatives, friends, cancer survivors and cancer support professionals. Certainly as a cancer nurse reading this book, it provided me with greater insight into the many additional and ongoing challenges faced by cancer patients once they leave the treatment environment, as well as how we as health professionals communicate to patients and carers and the impact our words can have.

While much of the literature is referred back to research studies, the referencing to specific studies is inconsistent and lacking in detail. From a health professional's perspective, I would recommend a more detailed reference list be used for future editions, particularly in today's environment of ensuring practice is based on evidence from quality sources.

From the perspective of the non-health professional, the regular references to research studies, as well as endorsement by the New Zealand Cancer Society would also be reassuring in the knowledge that the information is reliable and accepted within the conventions of today's medical arena.

The book is divided into four parts:

Part 1 – Put your diagnosis into perspective is an excellent overview of what cancer is, the impact of our immune system, the reactions of others to your cancer diagnosis, how your individual point of view can affect your recovery and how your emotional expression can affect your ability to cope.



Part 2 – Taking action to support healing discusses: the pros and cons of the four cancer treatment models, involving various combinations of conventional and complementary/alternative medicine; lifestyle habits such as sleep, diet and nutrition, weight management, exercise and activity; smoking, alcohol, caffeine and sun intake; sexuality; relaxation and meditation; cancer support groups; your healing team network; active hope and faith; the impact of language; and techniques such as visualisation and affirmation.

Part 3 – Explore and express yourself provides the tools to create your future, involving aspects such as developing a "life vision statement", subsequent goals and a plan as to how you will achieve them. The enthusiasm and vitality demonstrated by Kerslake, through the relaying of his personal experiences, provides the encouragement to really give this a go. This section of the book then leads into other actions you can incorporate to complement your life plan, such as humour, writing and music.

Part 4 – Life after cancer discusses post treatment challenges and how the tools in the book can still have a positive impact after treatment has finished. Kerslake provides a concise summary of all the recommendations made throughout the book and reinforces the power of action in overcoming fears and procrastination.

Overall, this is a book that I believe can make a real difference in the lives of cancer patients from all walks of life, and one that I would certainly recommend to patients to incorporate as part of their recovery process. The tools used in this book are also ones that can assist us all in achieving a greater mind, body and spirit balance, both in illness or wellness.

Susan Adams,
Greenslopes Private Hospital, Brisbane, Queensland.

A Practical Guide to Human Cancer Genetics 3rd Edition

Shirley V. Hodgson, William D. Foulkes, Charis Eng and Eamonn R. Maher
Cambridge University Press, 2007
ISBN: 0-521-68563-X
395 pages
RRP: \$150.00

This is the 3rd edition of this book by three well-known experts in the field of cancer genetics. Genetics is a continuously evolving area of medicine and this book presents us with high-quality information on the subject matter. As the title suggests, this is a practical guide to cancer genetics, but particularly relevant regarding known inherited disorders predisposing to cancer.

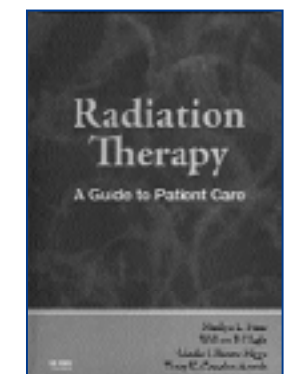
The content of the book is well set out; the first chapter describes various computer models that are available for assessment of cancer risk and an overview of the issues that are required to be addressed in a genetic counselling consultation. The authors describe a model of practice whereby clinics may increasingly be led by specialist cancer genetic nurses, but this is not a model of practice used within Australia. While not currently relevant, services may be developed in the future whereby the model of using specialist cancer genetic nurses' skills would be appropriate.

The second part of A Practical Guide to Human Cancer Genetics deals with inherited cancers by site of origin, dealing with a range of cancers both common and uncommon that may arise in a particular system. Each chapter comprehensively addresses the familial incidence of particular cancers and outlines the possible germline genetic basis, as well as the pattern of inheritance; where possible it gives screening recommendations.

The third part of the book explores in detail a range of known inherited cancer syndromes. It provides comprehensive molecular information on the development of these rare syndromes and offers recommendations for medical management where evidence exists.

The information provided in the book is current and comprehensive and is demonstrated by the extensive list of references. It will be of interest to all working in the area of cancer genetics/family cancer clinics.

Mary Shanahan,
Clinical Genetics Service,
Peter MacCallum Cancer Centre, Melbourne, Victoria.



Practical Hematopoietic Stem Cell Transplantation

Andrew J. Cant, Angela Galloway, Graham Jackson
 Blackwell Publishing 2007
 ISBN – 13:978-1-4051-3401-9
 205 pages plus Index
 RRP: \$229.00

This UK publication was printed in 2007 and the majority of the text is relevant to transplantation in Australia. There are three editors; Professor Cant is a consultant paediatric immunologist, Dr Galloway is a consultant microbiologist and Dr Jackson a consultant haematologist. There are 24 contributors ranging in fields of knowledge, including medical and nursing.

The layout is clear and the language coherent and concise. The index outlines the 17 chapters that explore the process of stem cell transplantation.

The first chapter gives a brief historical perspective and looks at the basic principles of hematopoietic stem cell transplantation. It then shows the indications for transplantation by looking at the diseases separately, including those in children. The second chapter discusses pre-transplant assessment including tissue typing/donation and investigations.

Chapter 3 looks at the transplant itself. It explores the types and choice of donor and sources of harvested stem cells. It discusses the different types of chemotherapy conditioning regimes and the common side-effects the patient may experience.

Chapter 4 gives accurate, current information related to caring for transplant patients. It looks at the different aspects of care and also gives some nursing interventions.

The following chapters describe the complications of transplant-related infections, the role of the intensive care unit, graft versus host disease, follow-up care and the future of stem cell transplants.

Each chapter starts with an introduction, followed by clear headings and ends with a conclusion, acknowledgements, further readings and useful contacts. At the beginning of the book there is also a thorough list of abbreviations. Whilst it is an informative book, some of the more complex sections are very brief

in content and would require further in-depth reading from other sources. However, it is a good introductory text and looks at pre and post-transplant care, including social and psychological aspects.

In summary, I found this book to be an accurate, informative overview of what is considered a complex treatment option. I would highly recommend it as a teaching tool for new and junior staff members. It could also be beneficial as a refresher for all health professionals involved in the area of stem cell transplantation.

Kirstin Fellenberg,
 Haematology and Bone Marrow Transplant Unit, Royal Adelaide Hospital, SA.

Radiation Therapy: A guide to patient care

Marilyn L Haas, William P Hogle, Giselle J Moore-
 Higgs, Tracy K Gosselin-Acomb
 Mosby Elsevier 2007
 ISBN: 978-0-323-04030-3
 743 pages
 PPR: US\$74.95

Radiation Therapy: A Guide to Patient Care is claimed to be a book for the radiation oncology nurse to assist in her role while caring for the patient with cancer. As a radiation oncology nurse I found the book very informative. The information it contains will truly help the novice nurse, starting anew in radiation oncology and for those who need to go into more detail on radiation cancer treatment. The book has a vast range of information on cancer care. It starts with the basics of radiation and its evolution, describing the different uses of radiation oncology with up-to-date information. Explanation of different types of radiation sources, such as brachytherapy, are well presented for even the novice practitioner. This book would be a good resource for those nurses working in different areas of oncology, as it is not just a book about radiation but a book about cancer and its different treatments and management.

Chapter 4 'Diagnosis and Staging' and chapter 5 'Simulation and Treatment Planning' are of great interest and easy to understand. These chapters provide useful information for the reader of what is really needed when a patient is diagnosed with cancer. It continues

AUSTRALIA AND NEW ZEALAND

Date	Name of Meeting	Place	Secretariat
2007			
November			
14-16	Clinical Oncological Society of Australia (COSA) 34th Annual Scientific Meeting	Adelaide SA	DC Conferences Tel: +61 2 9954 4400 Fax: +61 2 9954 0666 Email: cosa@dcconferences.com.au Web: http://dcconferences.com.au/cosa/
2008			
April			
30 – 2	New Directions in Leukaemia Research	Sunshine Coast, QLD	NDLR 2008 Red Hill, QLD Tel: +61 7 3368 2644 Fax: +61 7 3369 3731 Email: ndlr@ccm.com.au Web: www.ndlr2008.com
9 – 11	9th Behavioural Research in Cancer Control Conference	Melbourne, VIC	Centre for Behavioural Research in Cancer The Cancer Council Victoria Carlton, VIC Tel: +61 3 9635 5468 Fax +61 3 9635 5380 Email: brccconference2008@cancervic.org.au Web: www.brccconference2008.org.au
May			
18 – 21	41st Australasian College of Dermatologists (ACD) Annual Scientific Meeting	Sydney NSW	Australasian College of Dermatologists Boronia Park, NSW Tel: +61 2 8765 0242 Email: admin@dermcoll.asn.au Website www.dermcoll.asn.au
July			
25 – 26	Sydney Cancer Conference 2008	Sydney, NSW	The Conference Secretariat Cancer Research Network University of Sydney, NSW Tel: +61 2 9036 6309 Fax: +61 2 9515 3555 Email: sydneycancerconference@med.usyd.edu.au Web: www.cancerresearch.med.usyd.edu.au/
SCC2008/			
August			
6 – 9	Medical Oncology Group Australia (MOGA) Annual Scientific Meeting	Christchurch New Zealand	Medical Oncology Group of Australia Sydney, NSW Tel: +61 2 8247 6207 Fax: +61 2 9247 3022 Email: moga@moga.org.au Web: www.moga.org.au
September			
4 – 6	Australian and New Zealand Head and Neck Society (ANZHNS) 10th Annual Scientific Meeting	Melbourne, VIC	Royal Australian College of Surgeons Tel: +61 3 9249 1273 Fax: +61 3 9276 7431 Email: conferences.events@surgeons.org Web: www.anzhns.org
24 – 27	Australian and New Zealand Society of Palliative Medicine (ANZSPM) Conference	Darwin NT	ANZSPM Conference Darwin, Northern Territory Tel: +61 2 4973 6573 Fax: +61 2 4973 6609 Email: anzspm@willorganise.com.au Web: http://www.willorganise.com.au/anzspm08

INTERNATIONAL

Date	Name of Meeting	Place	Secretariat
2007			
October			
28 – Nov 1	49th ASTRO Annual Meeting	Los Angeles US	American Society for Therapeutic Radiology and Oncology (ASTRO) Fairfax United States Tel: +1 703 502 1550 Fax: +1 703 502 7852 Email: meetings@astro.org Web: www.astro.org
30 – Nov 3	2007 International Society of Paediatric Oncology (SIOP) Annual Congress	Mumbai India	SIOP 2007 – International Society of Paediatric Oncology Local Organising Committee 37/900, Adarsh Nagar Century Bazaar, Worli 400 030 Mumbai Tel: +91 22 24 38 10 68 Email: siop2007@variance.com Web: www.siop2007.in
November			
1 - 2	International Research Conference on Food, Nutrition and Cancer	Washington DC US	American Institute for Cancer Research (AICR) World Cancer Research Fund International Washington DC United States Tel: +1 202 328 7744 Fax: +1 202 328 7226 Email: aicrweb@aicr.org Web: www.aicr.org
3 – 10	24th International Papillomavirus Conference and Clinical Workshop	Beijing China	Chinese Medical Association c/o International Convention Services Beijing, China Tel: +86 10 8515 8149 Fax: +86 10 6512 3754 Email: ipv2007@cma.org.cn Web: www.ipv2007.org
7 – 9	Cancer in the Developing World	Cairo Egypt	National Cancer Institute, Cairo University Cairo, Egypt Tel: +20 2 535 1424 Fax: +20 2 532 8286 Email: a.badran@link.net Web: www.nci.edu.eg
8 – 10	Geriatric Oncology: Cancer in the Elderly	Madrid Spain	Society for Geriatric Oncology (SIOG) Genolier Switzerland Tel: +41 22 366 9106 Fax: +41 22 366 9131 Email: siog@genolier.net Web: www.cancerworld.org/siog
9 – 11	2007 Oncology Nursing Society (ONS) Institutes of Learning	Chicago US	Oncology Nursing Society (ONS) Pittsburgh, PA United States Tel: +1 866 257 4667, +1 412 859 6100 Fax: +1 877 369 5497, +1 412 859 6162 Email: customer.service@ons.org Web: www.ons.org

Date	Name of Meeting	Place	Secretariat
10 – 14	International Conference on Clinical PET and Molecular Medicine	Bangkok Thailand	International Atomic Energy Agency (IAEA) Vienna Austria Tel: +43 1 2600 Fax: +43 1 2600 7 Email: ipet2007@iaea.org Web: www.iaea.org
12 – 14	Cancer 2007: From Molecular Biology to Treatment 8th Sao Paulo Research Conference	Sao Paulo Brazil	University of Sao Paulo Sao Paulo Brazil Tel: +55 11 3361 3056 Fax: +55 11 3361 3089 Email: eventus@eventus.com.br Web: www.eventus.com.br/bioconferences
15 – 17	Making Connections: A Canadian Cancer Research Conference celebrating NCIC's 60th Anniversary	Toronto Canada	National Cancer Institute of Canada (NCIC) c/o DR Dunlop & Associates Ottawa Canada Tel: +1 613 235 8879 Fax: +1 613 235 0094 Email: dunlopdr@rogers.com Web: www.ncic.cancer.ca
15 – 17	19th Asia Pacific Cancer Conference (APCC) 2007	Tehran Iran	Tehran University of Medical Sciences Department of International Relations PO Box 14155-6559 Tehran Tel: +98 21 649 1070 Fax: 98 21 641 9537 Email: office@sina.tums.ac.ir Web: http://www.tums.ac.ir/about/index.html
22 – 23	8th International Netherlands Cancer Institute Head and Neck Symposium	Amsterdam Netherlands	The Netherlands Cancer Institute Amsterdam Netherlands Tel: +31 20 512 2550 Fax: +31 20 512 2554 Email: kno@nki.nl Web: www.hoofdhals.nki.nl
25 – 28	2nd International Cancer Control Congress	Rio de Janeiro Brazil	National Cancer Institute (INCA) c/o International Conference Services Vancouver Canada Tel: +1 604 681 2153 Fax: +1 604 681 1049 Email: cancercontrol2007@meet-ics.com Web: www.cancercontrol2007.com
25 – 30	RSNA 2007: Radiological Society of North America Annual Meeting	Chicago US	Radiological Society of North America (RSNA) Oak Brook United States Tel: +1 630 571 2670 Fax: +1 630 571 7837 Email: kchristianson@rsna.org Web: www.rsna2007.rsna.org
26 – 27	BASO-ACS and ABS at BASO Joint Scientific Conference	London UK	BASO – the Association of Cancer Surgery London United Kingdom Tel: +44 20 7405 5612 Fax: +44 20 7404 6574 Email: admin@baso.org.uk Web: www.baso.org.uk/content/acs-Meetings.asp
29 – 30	Cell Signalling and Novel Cancer Therapeutics	London UK	British Association for Cancer Research (BACR) Sutton

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
			United Kingdom Tel: +44 20 8722 4208 Fax: +44 20 8770 1395 Email: bacr@icr.ac.uk Web: www.bacr.org.uk/scientificmeetings/meetingdetail.asp?id=58
December			
1 – 5	47th American Society for Cell Biology Annual Meeting	Washington DC US	American Society for Cell Biology (ASCB) Bethesda United States Tel: +1 301 347 9300 Fax: +1 301 347 9310 Email: ascbinfo@ascb.org Web: www.ascb.org/meetings/index.cfm
5 – 8	6th Annual AACR International Conference: Frontiers in Cancer Prevention	Philadelphia PA US	American Association for Cancer Research, 615 Chestnut Street 17th Fl Philadelphia PA 19106-9165 Tel: +1 215 440 9300 Fax: +1 215 351 9165 Web: http://www.aacr.org/
2008			
February			
5 – 8	19th International Congress on Anti Cancer Treatment	Paris, France	ICTACT Organising Committee Paris France Ph: 33 (0) 1 42 16 05 16 Fax: 33 (0) 1 42 16 04 99 Email: v.blanchard@icact.com Web: www.icact.com/
8 – 10	XVth International Conference of the Indian Association of Palliative Care	Kerala India	Conference Secretariat Kerala India Tel: +91 48423 49764 Fax: +91 93492 92094 Email: kochipallcon@rediffmail.com Web: http://www.palliumindia.org/pallcon/index.htm
25 – 27	International Conference on Burkitt Lymphoma and Related Lymphoproliferative Disorders	Kampala Uganda	Department of Pathology and Human Oncology University of Siena Siena Italy Tel: +39 0577 232 000 Fax: +39 0577 232 134 Email: servcong@unisi.it Web: www.unisi.it/eventi/burkitt
26 – 28	Childhood Cancer: In Quest of a Complete Cure 5th SIOP Asia Conference	Muscat Oman	International Society of Paediatric Oncology (SIOP) c/o Informed Events Dubai United Arab Emirates Tel: +971 4 268 9040 Fax: +971 4 269 89030 Email: ifodub@emirates.net.ae Web: www.infomedweb.com/ourevents/SIOP2008/index.htm
27 – 01 March	14th Society for Research on Nicotine and Tobacco Annual Meeting	Portland US	Society for Research on Nicotine and Tobacco (SRNT) Madison United States Tel: +1 608 443 2462

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
			Fax: +1 608 443 2474 Email: meetins@srnt.org Web: www.srnt.org
28 – 2 March	5th American Psychosocial Oncology Society (APOS) Annual Conference	Irvine US	American Psychosocial Oncology Society (APOS) Charlottesville, VA United States Tel: +1 434 293 5350 Fax: +1 434 977 0899 Email: aball@apos-society.org Web: www.apos-society.org
March			
27 – 29	6th European Oncology Nursing Society (EONS) Spring Convention	Geneva Switzerland	Federation of European Cancer Societies (FECS) Brussels Belgium Tel: +32 2 775 0201 Fax: +32 2 775 0200 Email: EONS@fecss.be Web: www.fecss.be
April			
15 – 19	EBCC 6: 6th European Breast Cancer Conference	Berlin Germany	EORTC – EUSOMA – Europa Donna c/o Federation of European Cancer Societies (FECS) Brussels Belgium Tel: +32 2 775 0201 Fax: +32 2 775 0245 Email: EBCC6@fecss.be Web: www.fecss.be/emc.asp?pagelid=1309
May			
28 – 31	5th Research Forum of the European Association for Palliative Care (EAPC)	Trondheim, Norway	EAPC Head Office National Cancer Institute Milan Italy Tel: +39 02239 03391 Fax: +39 02239 03393 E-mail: heidi.blumhuber@istitutotumori.it Web: http://www.eapcnet.org/Research2008/Index.html
30 – 3 June	44th ASCO Annual Meeting	Chicago US	American Society of Clinical Oncology (ASCO) Denver, VA United States Tel: +1 703 299 0158 Fax: +1 703 299 0255 Email: meetings@asco.org Web: www.asco.org
June			
4 – 7	10th International Conference on Malignant Lymphoma	Lugano Switzerland	Istituto Oncologico della Svizzera Italiana (IOSI) Viganello-Lugano Switzerland Tel: +41 91 922 0575 Fax: +41 91 922 2084 Email: Cristiana.brentan@lymphcon.ch Web: www.lymphcon.ch

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
4 – 8	5th World Conference on Breast Cancer	Winnipeg US	Canadian Breast Cancer Foundation Port Robinson, ON Canada Tel: +1 905 384 1848 Fax: +1 905 384 1675 Email: mail@wcbcf.ca Web: www.wcbcf.ca/winnipeg08.php
9 – 13	10th World Congress of Psycho-Oncology	Madrid Spain	International Psycho-Oncology Society (IPOS) Charlottesville United States Tel: +1 434 293 5350 Fax: +1 434 293 5350 Email: info@ipos-society.org Web: www.ipos-society.org
July			
5 – 8	EACR 20: European Association for Cancer Research Conference	Lyon France	Federation of European Cancer Societies (FECS) Brussels Belgium Tel: +32 2 775 0246 Fax: +32 2 775 0200 Email: EACR20@fecfs.be Web: www.eacr.org, www.fecfs.be
August			
17 – 21	15th International Conference on Cancer Nursing	Singapore	International Society of Nurses Cancer Care International Conference on Cancer Nursing Secretariat Email: info@isncc.org Web: www.isncc.org
17 – 22	12th World Congress on Pain	Glasgow Scotland	International Association for the Study of Pain (IASP) Seattle, WA, United States Tel: + 206 547 6409 Fax: +1 206 547 1703 Email: iaspdesk@iasp-pain.org Web: www.iasp-pain.org/2008Congress.htm
27 – 31	UICC World Cancer Congress 2008	Geneva Switzerland	UICC Congress Secretariat 62, route de Frontenex 1207 Geneva Switzerland Tel: +41 22 809 1811 Fax: +41 22 809 1810 Email: congress08@uicc.org Web: www.uicc.org/congress08
September			
10 – 13	ESSO 2008: 14th Congress of the European Society of Surgical Oncology	The Hague Netherlands	Federation of European Cancer Societies (FECS) Brussels Belgium Tel: +32 2 775 0246 Fax: +32 2 775 0200 Email: ESSO2008@fecfs.be Web: www.esso-surgeonline.be
12 – 16	33rd European Society for Medical Oncology Congress	Stockholm Sweden	European Society for Medical Oncology (ESMO) Viganello-Lugano Switzerland Tel: +41 91 973 1919 Fax: +41 91 973 1918 Email: congress@esmo.org Web: www.esmo.org

CALENDAR OF MEETINGS

Date	Name of Meeting	Place	Secretariat
October			
1 – 6	SIOP 2008: 40th Congress of the International Society of Paediatric Oncology (SIOP)	Berlin Germany	SIOP Secretariat, c/o MCI Berlin Office Berlin Germany Tel: +49 30 20 4590 Fax: +49 30 20 45 950 Email: siop2008@cpb.de Web: www.siop2008.de
19 – 23	32nd World Congress of the International Society of Haematology	Bangkok Thailand	International Society of Haematology (ISH) c/o Ramathibodi Hospital Bangkok Thailand Tel: +66 2 201 1785 Email: webmaster@ish2008.org Web: www.ish2008.org
21 – 24	20th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics	Geneva Switzerland	Federation of European Cancer Societies (FECS) Brussels Belgium Tel: +32 2 775 0246 Fax: +32 2 775 0200 Email: iena2008@fecfs.be Web: www.fecfs.be
25 – 28	12th Biennial International Gynaecologic Cancer Society Meeting	Bangkok Thailand	International Gynaecologic Cancer Society c/o Kenes International / IGCS 12 Geneva Switzerland Tel: +41 22 908 0488 Fax: +41 22 732 2850 Email: igcs-12@kenes-com Web: www.igcs.org

THE CANCER COUNCIL AUSTRALIA

The Cancer Council Australia is the peak national cancer control organisation. Its members are the leading state and territory Cancer Councils, working together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.



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The Cancer Council New South Wales
The Cancer Council Northern Territory
The Cancer Council Queensland
The Cancer Council South Australia
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CLINICAL ONCOLOGICAL SOCIETY OF AUSTRALIA INC

The Clinical Oncological Society of Australia (COSA) is a multidisciplinary society for health professionals working in cancer research or the treatment, rehabilitation or palliation of cancer patients.



It conducts an annual scientific meeting, seminars and educational activities related to current cancer issues. COSA is affiliated with The Cancer Council Australia.

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Gastrointestinal Oncology

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Lung Oncology

Medical Oncology

Melanoma and Skin

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Urologic Oncology

MEMBERSHIP

Further information about COSA and membership applications are available from:

www.cosa.org.au or cosa@cancer.org.au

Membership fees for 2007

Ordinary Members: \$160

Associate Members: \$100
(includes GST)