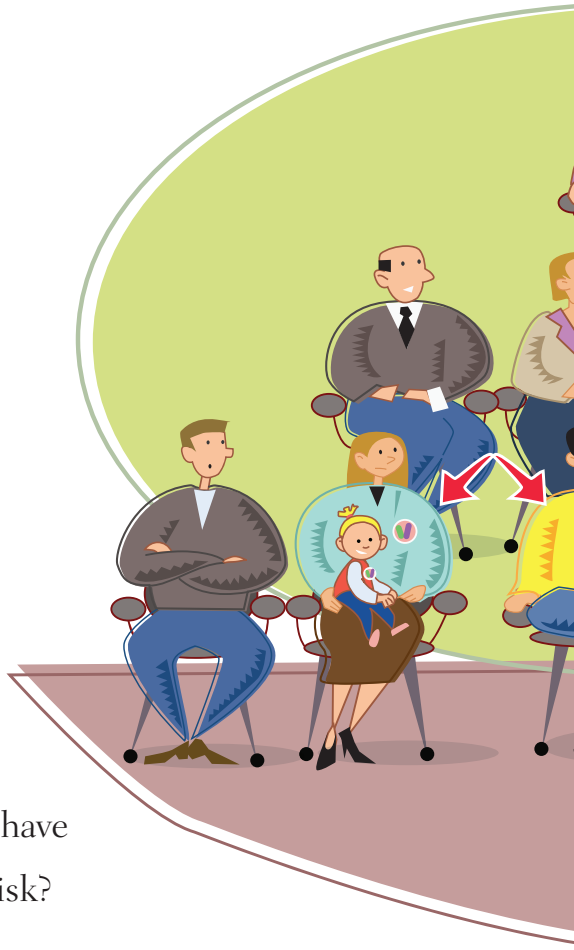
# Promoting genetic literacy: cancer control in the BRCA era



Anna Wagstaff

As more is learned about inherited genetic mutations that make cancers more likely, there is an acute need to give those who live with the mutated genes clear information and accurate advice. But are health professionals equipped to look for signs of genetic predisposition, and do cancer services have the skills and expertise to help people manage their cancer risk?

The hereditary nature of some cancers has been known about for more than a century. Familial adenomatous polyposis, which inevitably develops into colorectal cancer if left untreated, was first described in 1859 with the first note of familial association in 1882. The first recorded operation for polyposis was performed by Lockhart-Mummery at St Mark's Hospital in London in 1918. By 1927 a registry for families with this syndrome opened at the same hospital, effectively establishing the first genetic cancer clinic, to keep a watch over those at high risk. By the 1940s, management of the condition moved towards prevention, as surgeons began to remove much of the affected bowel before the onset of cancer.

All cancers, by definition, involve gene mutations, the discovery of which has kept cancer researchers busy for decades, offering a stream of targets for the development of personalised therapies. In the case of genetic predisposition, however, the mutation is not just in the cancerous cells, but in the germline, meaning that it is carried in the DNA which forms part of a family's gene pool, and is passed down the generations.

The mutated gene may be 'high-penetrance', in which case carriers are very likely to develop the associated syndrome. In the case of the mutated *APC* gene associated with familial adenomatous polyposis, carriers are almost 100% certain to develop colorectal cancer by the age of 40 unless they act to lower their risk. Other inherited syndromes, however, such as the hereditary breast ovarian cancer syndrome linked to harmful mutations in the *BRCA1* and *BRCA2* genes, have a lower penetrance, meaning that carriers are much more likely than the general population of women to develop breast and ovarian (and other) cancers, yet they may remain free of cancer all their lives.

In the twenty years that have passed since scientists in Berkeley, California, identified the *BRCA* genes, a number of other germline mutations have been


identified that raise the carrier's risk of developing particular types of cancer (none as significantly as the *BRCA* mutations). The implications for the way society deals with cancer and professionals approach cancer control, are only now beginning to become clear.

## Learning to live with BRCA

Francisca Bach Kolling from the Netherlands describes herself as one of the 'first generation' of identified carriers of a harmful *BRCA* mutation. Diagnosed and treated for breast cancer in 1990, aged 41, it was not for several years that she became aware of media reports about the discovery of a 'breast cancer gene'. Her

**IN BRIEF**

- Accounting for around 5%–10% of all breast cancers, harmful mutations in *BRCA1* or *BRCA2* increase a woman's chance of developing breast cancer over their lifetime by approximately five times compared to the normal population.
- Carriers of the harmful *BRCA1/2* mutations are also approximately 10–30 times more likely to develop ovarian cancer, with these mutations accounting for around 10% of all ovarian cancers.
- There is no single *BRCA* mutation, but a wide variety of mutations on these two genes, many of which have yet to be recorded. Only some have been demonstrated to be harmful.
- *BRCA* mutations can also raise the risk of other cancers, including gastric, pancreatic, colon and prostate cancer, as well as melanoma and male breast cancer.
- Other 'cancer genes' include mutated *APC* genes, responsible for familial adenomatous polyposis, which lead to colon cancer, and mutated *MLH1, MSH2 MSH6*, or *PMS2* genes, which are associated with hereditary non-polyposis colon cancer (HNPCC), a syndrome that also raises the risk of endometrial (uterine), stomach, ovarian, small bowel (intestinal), urinary tract, liver, and bile duct cancers.

ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

## Hereditary predisposition to cancer is something you live with for the whole of your life

mother had been diagnosed with breast cancer at the age of 53, so she decided to get herself tested, despite protestations from her GP that there was no reason to suspect a genetic predisposition. As it turned out, she did carry a variant of the *BRCA1* gene mutation – but her mother did not. It was her father who had passed on the mutation – a possibility that is frequently overlooked.

At her pre-test counselling she learned that some mutations that raise the familial risk of breast cancer also make ovarian cancer up to 60% more likely. "That hit me hard. It was like being told I had cancer again."

Francisca weighed her options. Already the mother of three children, she decided to have her ovaries removed, which greatly reduced her risk of ovarian cancer (for which there is no effective surveillance) and somewhat lowered her breast cancer risk. She underwent regular breast MRIs to maximise the chance that any new breast cancer would be picked up at a very early stage. This strategy paid off as nearly three years later she did develop breast cancer in the opposite breast. She opted for a full mastectomy, and nine years on seems to be in the clear.

Francisca has no major complaints about the quality of counselling she received, She does feel, however, that two important aspects of hereditary cancer continue to be overlooked by genetic cancer services. The first is that a hereditary predisposition to cancer is something you live with for the whole of your life. "You get the information and the counselling to help you decide whether you want surgery or not, but they don't then monitor how you are doing with it. How are you coping? Do you need support?"

The second is that your own genetic test result also has profound implications for all your blood relations. This information could save lives, but could also generate major stress and tension, burdening relatives with the knowledge of risk factors they would have preferred to have remained ignorant about. Francisca feels the onus of deciding who to tell what about the family *BRCA* mutation was left entirely on her shoulders, and she would have welcomed more help and advice from the genetics services, including practical ideas on how to go about this, advice about what kind of reactions to expect, and the chance to talk afterwards about how it went.

Her husband was immensely supportive, and together they organised a special weekend with the children, then aged between 16 and 22, to tell them the news. Their immediate response, says Francisca, was sympathy for her, but they also seemed quite relieved. "They had been expecting something worse – maybe that we were going to get divorced or something!" It was only later that the implications for their own lives really dawned on the children.

These are the 'second generation' – asymptomatic children, nephews and nieces of the 'first generation' – who are now growing up, forming relationships, starting families, in the knowledge that they may have inherited the gene mutation. This generation, says Francisca, is facing difficulties and dilemmas her generation never had to. While supporting other people with hereditary breast cancer, she has learned about the friction that can build up between siblings when it turns out that some are lucky and escaped the gene mutation, while others are not and have a lifelong worry for themselves and for any children.

It is often when this 'second generation' are themselves at the point of having children that the issue of testing comes to a head. One young man who knew he may have inherited a *BRCA* mutation told Francisca that he and his partner had decided to have children "in the normal way", without being tested. "They hope that if the children are girls, medical research will find some way to avoid them facing those difficult options of today; that there may be a pill or something to stop you getting cancer." An optimistic attitude, comments Francisca, who herself tends to favour double mastectomy for maximum protection, at least in later years – an option she says is very popular among 'hard-headed' Dutch women.

## Young people who start new relationships struggle with the dilemma: 'When do I tell him/her?'

Another young man tested positive, and told her of the dilemma he faced in starting a family. He was thinking about trying to get a preconception genetic diagnosis, which involves screening an embryo *in vitro* before transferring it to the mother's uterus (a procedure available only in a few countries, and only where family history points to an exceptionally high risk). But he worried about what it would mean for his wife. "I am the carrier, we don't want to pass on the gene mutation to our children, but I have to ask my wife if she can take the burden, because it is quite a heavy procedure medically." Francisca herself wonders what she would have decided if she had known what she knows now when she was about to start her family.

The key, she says, is to find some sort of understanding and harmony with those you are living with. But relationships do not always last, in which case he or she may again face the responsibility of explaining about the mutation to a new partner, and trying to find way of living with that burden harmoniously. Francisca says that all young people in this position who start new relationships struggle with the dilemma: 'When do I tell him/her about my genetic predisposition?' "We have to give more attention to this group," she says, "because they are growing and they think about it quite differently to us."

Francisca is certainly trying to do her bit to help, by working with the Dutch Breast Cancer Organisation's advocacy group for hereditary breast/ovarian cancer, offering support and organising conferences. The group also campaigns to stop discrimination against mutation carriers, for instance by life insurance companies – an issue where they have scored some success. However, if you are a self-employed woman in the Netherlands, no-one will insure you against being unable to work if you know you carry the *BRCA* mutation.

**RIGHTS AND REGULATIONS ACROSS EUROPE**

The possibility of facing discrimination by employers, insurance companies, banks etc. can act as a serious deterrent to being tested for a genetic predisposition to cancer. Rights to privacy and duties of disclosure vary across the EU countries. The 154 page pamphlet: *Patients' rights, insurance and employment: A survey of regulations in the European Union* was published by the EU in 2002 (http://ec.europa.eu/research/biosociety/pdf/genetic_testing_eur20446.pdf), but this is now somewhat dated. A general protocol on genetic testing for health purposes was adopted by the Council of Europe in 2009 (see *Eur J Human Genet* 17:1374–1377).

## A NEW FIELD IN CLINICAL ONCOLOGY

While the personal and social impact of greater knowledge and awareness of individual risk has been profound, the implications for cancer control and care may be no less radical. Bernardo Bonanni, head of the division of cancer prevention and genetics at the European Institute of Oncology (EIO) in Milan, talks in terms of "a small revolution" that has opened a new field in clinical oncology.

"We are increasingly looking at risk assessment as the first thing to do. We have many more tools now, including genetics, to study the individual risk of each patient or cohort of subjects. We have risk managers, experts in cancer risk, and we have to train new experts in this field."

He would like to see cancer services develop strategies based on models similar to those now widely used to identify and manage people at risk of heart attack or stroke.

Bonanni is at pains to challenge the popular misconception that risk levels are divided into 'standard' or 'high'. There is in fact no such thing as *'the BRCA* mutation'. Several mutations have been recorded on the *BRCA1* and *2* genes, some of them apparently harmless, while the harmful ones pose varying degrees of risk. Raised risks for various cancers can also be passed on through mutations in other genes, while other conditions such as metabolic syndrome, which raises androgen levels, or even a family predisposition to obesity, can also raise the risk of cancer. A point Bonanni likes to emphasise is that the majority of those who are referred to his High Risk Clinic belong to what he terms 'the grey zone' – they have a clear family predisposition to cancer, but the culpable gene mutation, or combination of mutations, will probably never be found.

What it all adds up to, he concludes, is that we are all on a spectrum of cancer risk, influenced by a myriad of genes in the family gene pool, interacting, of course, with our own particular environmental and lifestyle risk factors.

Understanding the risks, he argues, opens up new possibilities for refocusing cancer control away from treating established disease towards prevention and early detection. Six-monthly breast MRI scans from the age of 25 make no medical or economic sense in the general population, but make perfect sense if you can identify women with a demonstrable risk of developing breast cancer at such an early age. The cost and side-effects of chemopreventive agents such as tamoxifen are only outweighed by the advantages when used in women at high risk.

For this refocusing of cancer services to become reality, three things need to happen, says Bonanni.

# Understanding the risks opens up new possibilities for prevention and early detection

- A network of multidisciplinary specialist clinics must be established, building on genetic clinics, but including oncologists, preventionists, geneticists, genetic counsellors, surgeons and other experts, who should discuss as a team the risk management plans for cases referred to them.
- The public, GPs, oncologists and other specialists need to become much more aware, to ensure that people understand their risk, get good advice on risk management, and are referred to specialist clinics as appropriate.
- A much greater focus is needed on developing and evaluating effective preventive strategies – a cancer equivalent of compounds already used as preventive agents, such as statins for heart disease.

Bonanni has been promoting all three. He argues for more and better teaching for oncologists and biologists to understand and practice risk assessment and risk reduction "exactly as cardiologists and internists do for their fields". In terms of service provision, he advocates for regional hubs of expert multidisciplinary risk management teams, working to agreed guidelines. His personal passion, however, is the development of preventive agents and strategies. He has been working for many years as part of a fairly small network of academic researchers who have swum against a tide of scepticism, but whose time may now be coming.

Bonanni's outlook is definitely closer to the young man hoping for 'a pill' than to Francisca and her generation in the Netherlands, who have largely opted for surgery. The reality is, however, that the evidence base for prevention is still very much work in progress, not least because proving that an intervention significantly reduces the risk of developing cancer takes more time and money and a bigger population study than proving treatment efficacy. "This is an ongoing field," says Bonanni. "We always share with people very clearly what is certain and what is uncertain so far. And this honesty is welcomed by them."

One area of growing certainty, says Bonanni, is the efficacy of regular breast MRI in picking up tumours in time to stop them spreading (*Cancer* 113:3116–3120; *JCO* 24:5091–5097; *J Natl Compr Can Net* 8:562–594), so long as this is done in expert centres, with up-to-date equipment and expert radiologists. In premenopausal patients, he adds, it is important that the MRI is done during the second week of the menstrual cycle, something radiologists don't always know.

Studies have demonstrated the value

## When genetic testing goes bad

The importance of accessible expert genetic cancer services in the BRCA era has been highlighted by experience in the US, where private providers stand accused of mis-selling genetic testing to ill-informed medical professionals and individuals. Companies like Myriad, which was the first to clone the BRCA mutation, and whose claim to sole rights in the US to diagnose any BRCA mutation were largely invalidated by a US federal court judge last year, are charged with trying to circumvent cancer genetics clinics, pitching instead for referrals directly from GPs, most of whom do not really understand what they are dealing with. Equally worrying is the direct to consumer advertising – often with discounts offered if you can sign up other members of your family.

A recently published study conducted by the Yale Cancer Center (*Conn Med* 74:413–423), reported on a national US series of cases illustrating what can happen when cancer genetic testing is performed without counselling by a qualified provider. Three major patterns of bad outcomes emerged: wrong genetic test ordered; genetic test results misinterpreted; inadequate genetic counselling. The results, documented in the report, included:

- unnecessary prophylactic surgeries
- unnecessary testing
- psychosocial distress, and
- false reassurance resulting in inappropriate medical management.

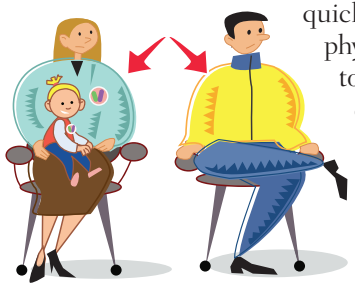
One family doctor consistently ticked the 'Jewish' box on the test form, thinking he was doing his patients a favour as it is easier to claim the costs for the *BRCA* test on insurance if you are Jewish. What he didn't realise is that there is a particular 'Jewish' *BRCA* mutation, and this was the only mutation that his patients were tested for.

of the selective oestrogen receptor modulators (SERMs) tamoxifen and raloxifene in risk reduction for ER+ breast cancers. The IBIS II study is investigating whether aromatase inhibitors can also be effective as preventive agents. An increasing literature also supports the beneficial role of the contraceptive pill in *BRCA* mutation carriers. Bonanni refers to a recent meta-analysis carried out by members of his department (*EJC* 46:2275–2284). "It shows the use of endocrine contraceptives in *BRCA* mutation carriers does not raise significantly the risk of breast cancer even if taken for a long time, but on the other hand it does decrease the risk of ovarian cancer by 50%."

"Of course SERMs don't cover the gap of ER-negative carcinogenesis," adds Bonanni. This is why research into other types of compound is so important." Such research includes everything from nonsteroidal anti-inflammatory drugs (NSAIDs) to statins and vitamins, especially vitamin D and retinoids, which are vitamin A derivatives. Much of this work has been funded so far by the US NCI, and led by pioneers like Michael Sporn, who first coined the term 'chemoprevention' (see *Cancer World* May–June 2006). But Europe has also made a contribution, not least Bonanni's team at the EIO, which has spent 20 years working on various potential chemopreventive agents, including fenretinide, a synthetic derivative of vitamin A. "A number of publications have found evidence of strong capability of this compound to reduce risk of breast cancer, and a good trend to reduce risk of ovarian too," says Bonanni. That evidence will be a lot clearer once the results of an ongoing phase III, double-blind placebo-controlled trial in women at high risk are known.

Bonanni is also enthusiastic about research into 'natural compounds' with cancer prevention properties, such as carcumin and green tea, and he believes advice on diet and exercise should be an integral part of cancer prevention.

As for the more radical options of risk-reducing surgery, Bonanni describes himself as 'a moderate', contrasting the approach of his department with what he calls 'extremists', who are quick to advise early prophylactic surgery "not only to gene mutation carriers." Though removing close to 100% of breast tissue has been shown to reduce risk even below the standard risk for non-mutation carriers, this can be hard to achieve even for experts, and the ideal of a zero risk level is unattainable, he argues.



There is more of a case to be made, he believes, for removal of the ovaries. "If you are still a fertile woman and have a risk of an ER+ cancer, as for example *BRCA*2 mutation carriers, removing the ovaries very early reduces your risk of breast cancer by around 50%. The primary drawback, of course, is that the woman loses her chance of having children through natural conception, which is one reason why Bonanni advocates a sequential approach to risk management, saving more radical options for later. "If you are at high risk, you can start sometimes very early in your lifetime with surveillance, which maybe should be increased over time. At a certain point, when the estimate of your risk increases, you may opt for a chemoprevention programme like entering a trial, and when these estimates increase further, you may need to go for a surgical prophylactic option."

For individual women and their medical advisers, adopting such a sequential approach in principle is only the first step. Getting the timing right can be tricky, and this is where knowledge of risks, risk reduction and counselling skills are so essential, and why Bonanni is advocating for specialist teams.

## A service for the BRCA era

Europe now faces the challenge of organising services that translate our new-found insight about genetic cancer risk and risk management strategies into effective prevention. The UK has been ahead of the game, setting up regional genetics services in the 1990s, many of which developed distinct cancer genetics services. Rachel Iredale, who works as a research fellow with the Cancer Genetics Service for Wales, stresses the unique nature of the genetics services model in healthcare.

The unit of care is the family rather than the individual, and the service does provide the sort of support Francisca lacked in discussing how to raise the issue of a genetic predisposition to cancer with other family members. They can even help, "for instance by writing to the GPs of family members to say that somebody in the family has a bowel cancer and it might be worth screening people."

Bonanni advocates a sequential approach to risk management, saving more radical options for later

# In the US people are encouraged to find out about their family history of cancer and take appropriate action

Another key aspect addresses Francisca's concern over long-term follow-up. "Once you are referred into the service you are with us for life," says Iredale. "We get a lot of 18-year-old women who have seen their mothers die of cancer, or their sisters or their aunts have got it, and they want to do something quite quickly. They can come for counselling, and they can re-access the service at any stage. As they get to particular milestones in their lives, when they want to get married or are thinking of having children, fears about cancer often re-emerge, so they can re-contact the service at any time."

Iredale has also been working with high-risk families to produce a series of around 50 digital stories (www.cancergeneticsstorybank.co.uk) to help people in similar situations, answering questions like: "What is it like to have a genetic counselling appointment?" "What feelings will I have if I go for genetic testing?" "How will I tell my kids that cancer is running in our family?"

Raising awareness among GPs, oncologists and other health professionals about the need to look for a family history of cancer is also part of the genetics services remit. "We have two questions that we give that are very sensible and a six-year-old could understand:

- Are there two or more close relatives with cancer on the same side of the family?
- Has any relative been under 45 when diagnosed with cancer?

What the service doesn't do, for the moment, is the sort of 'directive' public health work that is becoming common in the US, which encourages people to take responsibility for their own health by finding out about their family history of cancer and taking appropriate action. One suggestion from the US Surgeon General has been for people to discuss these issues when they gather at family occasions such as Thanksgiving – the so-called 'turkey talk'. The advocacy group FORCE – Facing Our Risk of Cancer Empowered – also aims to help people find out about their risk level and use that information to help them stay healthy.

The turkey talk. Finding out about the conditions and diseases that run in your family is a step everyone can take towards managing risks to their own health

Iredale is convinced that this is the way Europe needs to start thinking in the BRCA era. "Because we know more and more about the genetic components of common conditions, like heart disease, diabetes, asthma, there is a shift within certainly the academic and clinical communities to try to get people to use this information for health promotion and promoting good public health. We call it acquiring a genetic literacy."

She would like to see this public education start at primary school age, and has written a research proposal that could be the first step in moving towards the more proactive US 'empowerment' model. "Children need to know what role genetics plays in their family. And they need to learn that genetics isn't a scary word, cancer isn't a scary word, and they can have a lot of it in their families. They need to use that information in a way that helps them and encourages them to make good diet, lifestyle and reproductive decisions."