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Women born before 1940 have a much lower risk of developing breast cancer than their daughters.

GENETICS

Relative risk

Mutations in BRCA *genes predispose women to cancer, but outside influences shape the ultimate risk.*

BY MOISES VELASQUEZ-MANOFF

In 1990, geneticist Mary-Claire King forever transformed how we think about cancer with a single discovery: a mutation that dramatically increased carriers' risk of ovarian and breast cancer[1]. The gene *BRCA1* codes for a protein that is important in DNA repair. The mutated version impairs defences against tumours, increasing the lifetime risk of breast cancer in King's cohort to more than 80%, and the risk of ovarian cancer to as high as 40–65%. By comparison, the risk in the general population is 12% for breast cancer and 1.3% for ovarian cancer.

Four years later, another group identified a mutation in a second gene — *BRCA2* — that also elevated the risk of these cancers, although by less. Mutations in the two *BRCA* genes are now thought to account for between 5 and 10% of all breast cancers, and 15% of ovarian cancers. These discoveries stand as landmark successes of the genomic era.

Although testing women for *BRCA* mutations is now commonplace for women with a family history of the disease (see 'Should all women be tested?'), the path between mutation and cancer is complex. Some studies show that the risk from *BRCA* mutations varies among different populations, suggesting that any particular woman's fate depends on more than just her genes[2]. Among women who carry the mutation, additional factors — including exposure to oestrogen — may shape the risk of disease. Understanding the interplay between genes and the environment could illuminate the ultimate origins of breast cancer, possibly leading the way to new strategies for prevention and treatment.

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UNEQUAL RISKS

Some of the disparity in the risk from *BRCA* mutations is generational. One repeated finding is that, by age 50, mutation carriers born in the early twentieth century seem to have a lower risk of cancer than those born later[3]. The pattern suggests that outside influences interact with genes, and that something in the environment has changed in an unfavourable way. If researchers can figure out what those influences are, and why they have increased disease prevalence, maybe in the future they will gain new, less invasive tools to delay disease onset — and possibly prevent hereditary cancers altogether.

In 2003, King persuasively showed that the link between *BRCA* mutations and the risk of cancer varied with time. For Ashkenazi Jewish carriers born after 1940, the likelihood of developing breast cancer by age 50 was nearly triple that of women born before that date. "These people can be in the same family," says King, who is at the University of Washington, Seattle. "This is not genetic. The whole risk curve is getting shoved younger." This 'cohort effect' has been replicated by numerous researchers over the years, but its meaning is debated.

King attributes the generational shifts in *BRCA*-associated risks primarily to two trends: earlier starts to menses, and later first pregnancies. Women have been delaying first pregnancies more and more over the course of the past century. Meanwhile, girls now have their first menstruation about two years earlier than they did in the late nineteenth century.

Together, earlier menarche and later first pregnancy have increased the average woman's exposure to the sex hormone oestrogen, which is thought to promote tumour survival and growth. King believes this lengthened period of oestrogen exposure increases the risk of hereditary and non-hereditary cancers alike.

WESTERNIZED HORMONES

Other researchers, however, think it is important to understand how our overall hormonal milieu may have changed over the past 100 years or so. Gillian Bentley, an anthropologist at Durham University in the UK who studies Bangladeshi immigrants, thinks that society-wide shifts could partly explain the increase of cancer during the past century both in *BRCA* mutation carriers and non-carriers.

One line of evidence is that the reproductive hormone levels of Bangladeshi immigrants vary according to when the women arrived in the United Kingdom. For those who came before puberty, adult hormone levels are similar

to native-born Britons. But if they arrived after puberty, their hormone levels remain suppressed relative to native Britons, but similar to levels of women in Bangladesh. Accordingly, South Asian immigrants who arrived as adults tend to develop breast cancer less often than native Britons. But their British-born children have a risk closer to native Britons. "They're all from the same genetic background. We match them in terms of region of origin. And they move environments, and they look completely different," she says. "What does that say about genes?"

Bentley suspects that childhood infections probably hamper the supply of reproductive hormone levels in people who grow up in Bangladesh. Because such infections were common throughout all societies in the past, it is possible that a similar scenario protected previous generations of western women from breast cancer. The lesson, however, is not to reinstate early-life infections, but to remember that genes interact significantly with the environment, Bentley says. "We need to understand the complexities," she says, "and not be too simplistic in saying that genes determine your destiny."

MUTATION SCREENING

Should all women be tested?

Last year, Mary-Claire King, the geneticist who discovered the link between *BRCA* mutations and an increased risk of breast and ovarian cancer, and her colleagues argued in the *Journal of the American Medical Association* that all women should be screened for mutations in *BRCA1* and *BRAC2* (ref. 6). This approach, she says, would give women who might not otherwise know they are carriers a chance to consider proactive steps, including preventive surgery.

Some are sceptical of King's proposal, however. Beverly Levine, a health policy expert at Wake Forest University School of Medicine in Winston Salem, North Carolina, says that the cost of such a programme per life saved would be forbiddingly high. She is concerned that universal testing might capture women with mutations who, because of little understood genetic or environmental interactions, actually have a low risk of cancer. But oncologists will still recommend that they undergo prophylactic surgery. "Any time you have to involve a large number of people to prevent one case of disease," Levine says, "there are unintended consequences."

Such criticism does not faze King. Variants of unknown significance simply should not be included in the test results, she says. As for expense, the cost of these tests is falling rapidly. By her estimation, it might take 300 tests to save one life. And at a cost of US$200 per test, she feels that the investment is worth the payoff. She is emphatic that younger women in particular need to get tested, even if they do not have breast or ovarian cancer in the family. "Women need to know," she says. "Their genes aren't going to go away." **M.V.-M.**

IMPROVING THE ODDS

Joanne Kotsopoulos, a cancer researcher at the University of Toronto in Canada, is trying to help women who carry a *BRCA* mutation by identifying steps that they can take to protect themselves. Overweight women tend to produce extra growth factors and sex hormones, so staying slim may be one option. In a cohort of nearly 1,100 women, Kotsopoulos found that *BRCA* carriers who had lost at least 4.5 kilograms between ages 18 and 30 had around half the risk of developing breast cancer by age 49 compared with carriers who did not lose weight. By contrast, the use of oral contraceptives before age 20 correlates with a 45% increased risk of cancer in *BRCA1* carriers by age 40 (but not ovarian cancer)[4]. Because of the protective effect of oral contraceptives against ovarian cancer, she advises carriers to begin taking them once they reach 25.

"There are lots of things you can't change about your genetics."

What most excites Kotsopoulos, however, is exercise. She was first inspired by King's 2003 study, which linked exercise in adolescence with a reduced risk of cancer later. In adults, exercise may lower breast-cancer risk by decreasing hormone and growth-factor levels. Regular physical activity in childhood can also delay menarche, shortening the period of oestrogen exposure. But Kotsopoulos suspects that exercise also helps in another way: by directly activating *BRCA* genes.

Many mutation carriers have one functioning *BRCA* gene. Exercise activates the functional copy sufficiently, Kotsopoulos thinks, to partly compensate for the non-functional copy[5]. In an, as yet, unpublished study, she found that sedentary mutation carriers have less *BRCA* gene expression than more active carriers.

These are just associations, she stresses. They require confirmation in prospective research, and further testing in intervention studies — they are not meant to replace preventive surgery for mutation carriers. Rather, Kotsopoulos' goal is to provide evidence-based advice to the significant number of patients who decline surgery. Eventually, however, understanding these 'soft-risk' modifiers may lead to new, less-invasive treatments, including drugs that mimic the *BRCA*-activating effects of exercise — an approach Kotsopoulos has begun testing in people.

A CARCINOGENIC MICROBIOME?

Mysteriously, however, even when researchers control for risk modifiers, such as body fat and physical activity, they still cannot completely abolish the cohort effect. All else being equal, older women still seem to have a lower lifetime risk of breast cancer than younger women. To explain the increase over time of breast cancer generally, some researchers are turning their attention to the human microbiome.

Susan Erdman, a microbiologist at Massachusetts Institute of Technology in Cambridge, suspects that diet- and antibiotic-driven shifts in our microbial communities have, by encouraging chronic inflammation, increased the risk of breast, ovarian and prostate cancer in westernized populations.

Erdman has proven the basic concept in animal models. In mice, a junk food diet can increase the risk of these malignancies, apparently by altering the microbiome and lowering the immune system's ability to halt inflammation.

In the future, Erdman says, therapeutically targeting the microbiome could help to lower cancer risk. "There are lots of things you can't change about your genetics," she says. "But there's lots you can change about your interaction with microbes."

Looking forward, scientists are trying to understand how cancers linked with *BRCA1* and *BRAC2* mutations interact with non-hereditary factors (as well as with other genes). Perhaps a better understanding of this interplay will allow oncologists to provide more precise, individualized risk assessments that reduce the number of unnecessary surgeries. And maybe one day carriers will know how to reliably, and meaningfully, alter their risk of developing breast cancer with interventions other than surgery.

For now, King says that the options for women carrying a *BRCA* mutation remain limited. They can either live with increased risk and fear, or they can get a preventive operation. "I wish there were interventions that were safe that we could use," she says. "We don't presently have a non-surgical intervention." ■

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