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Genetics: Relative risk

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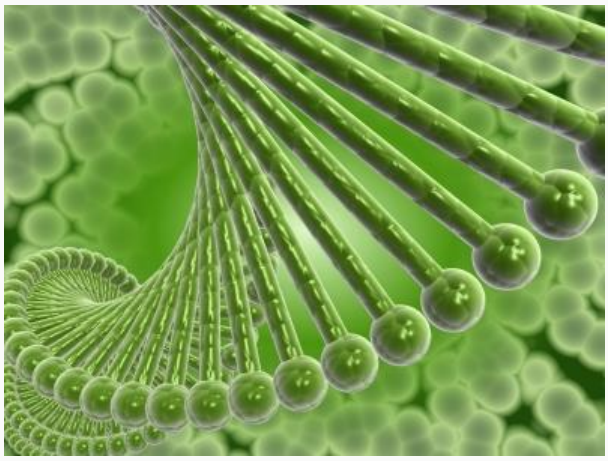

Mutations in BRCA genes predispose women to cancer, but outside influences shape the ultimate risk

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.

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.

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