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Family history and location of genetic fault affect risk for carriers of cancer genes

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A large scale study of women carrying faults in important cancer genes should enable doctors to provide better advice and counselling for treatments and lifestyle changes aimed at reducing this risk.

Cancer is caused by a combination of inherited genetic faults and environmental factors. While many hundreds of genetic mutations each increase an individual's risk by a small amount, faults in two particular genes - BRCA1 and BRCA2 - are known to greatly elevate the risk of breast and ovarian cancers.

The clinical management of women with faults in the BRCA1 and BRCA2 genes requires accurate estimates of their risk of developing breast cancer and how this changes with age. These can be used to estimate how prevention strategies such as medication, surgery and changing lifestyle factors reduce a woman's risk, and can assist with decisions about the age to commence cancer screening, hence enabling better-informed decision-making.

Almost all previous reports on cancer risks for BRCA1 and BRCA2 mutation carriers have been based on 'retrospective' studies - looking at women who had already developed cancer - and estimates are therefore susceptible to biases associated with such study designs, for example inaccuracies in family history reporting and assessment in women born many decades previously (when breast cancer incidence was much lower) that are not relevant to today's women.

Prospective cohort studies, in which scientists recruit and follow over time carriers of the mutations who have not yet developed breast cancer, overcome these issues. But the prospective studies of women with the BRCA1 and BRCA2 genes published to date have been very small, with the largest based on just 64 incident breast cancers.

Now, in a study published in *JAMA*: *The Journal of the American Medical Association*, an international team of researchers led by the University of Cambridge, UK, has recruited almost 10,000 mutation carriers for a prospective cohort study. This enabled the team to estimate more precisely the breast and ovarian cancer risks for women with faults in BRCA1 and BRCA2.

"We have been able to provide the most precise estimates of age-specific risks to date," says the study's lead author, Dr Antonis Antoniou from the Department of Public Health and Primary Care at the University of Cambridge. "These should provide more confidence in the counselling and clinical management of women with faults in the BRCA1 and BRCA2 genes."

The researchers found that 72% of women carrying a faulty BRCA1 gene will develop breast cancer risk and 44% will develop ovarian cancer by age 80. Similarly, they found that 69% of women carrying a faulty BRCA2 gene will develop breast cancer and 17% will develop ovarian cancer by age 80. However, for both cancers, a woman's family history affected the risk - in other words, if a woman's relative had had a breast cancer diagnosis, then her own risk would be higher than that of a carrier with no family history.

The researchers also found that the position of the specific fault within the gene affected the cancer risk. Mutations in genes occur when the 'letters' of DNA - A, C, G and T - get 'mistyped' and replaced with a different letter.

"The results show clearly and for the first time in a prospective study, that the cancer risks for women with faults in BRCA1 and BRCA2 depend both on the precise mutation and the woman's family cancer history," says Professor Douglas Easton, also from Cambridge and principal investigator of the UK-based EMBRACE study, the largest national cohort of women with mutations that contributed to the study.

Advances in sequencing technologies have opened up the potential of screening all women for BRCA1 and BRCA2 mutations, rather than just those with a significant family history of cancer, as is currently the case in the UK and most other countries. Such population-based screening, however, depends on having reliable estimates of risk to provide to women with and without a family history.

"Now that we understand more clearly the risks faced by women who carry these genetic faults, we would be in a better position to counsel them about the outcomes from screening and prevention programmes," says Professor Gareth Evans, Consultant in Medical Genetics and co-author from University of Manchester.

"This will also have practical implications on clinical management decisions, for example on the timing of surgery in order to reduce cancer risk. Such decisions tend to be taken around childbearing age, but some women with lower risks may opt to delay surgery until they complete their families."

The cancer risk estimates obtained by the present study were made possible because of over two decades of investment from Cancer Research UK, the European Union and other funders in establishing and following the cohorts.

Professor Arnie Purushotham, Cancer Research UK's senior clinical adviser, said: "Women who carry faulty BRCA genes are much more

likely to develop breast or ovarian cancers, and this large study could help women, and their doctors, better understand their risk of developing these cancers.

"This information - combining family medical history and the specific position of the faults in the BRCA genes - could help women decide the steps that they may want to take to reduce their risk of breast cancer, such as preventative surgery, medication or lifestyle changes."

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