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COMMENTARY

A new kind of breast cancer gene mutation

A Countercurrents Series[a]
with S.A. Narod MD

A fascinating article, recently published in *Nature* and titled "Mosaic *PPM1D* Mutations Are Associated with Predisposition to Breast and Ovarian Cancer" by Nazneen Rahman and her colleagues[1], is a rare example of a discovery that causes a re-evaluation of our assumptions about cancer and cancer genes.

The authors set out along a path well-travelled, intending to look for rare but highly penetrant gene mutations that might help to explain some of the residual heritability in breast and ovarian cancer—that is, to explain cancer families without a *BRCA* mutation. They used next-generation sequencing to study a panel of 507 genes connected in some shape or form to DNA repair. The experiment was an extension of earlier work, made possible by the new technology. The project was facilitated by the collection of 13,462 DNA samples from many patients over many years (attesting to the prescience of the British funding authorities; I suspect that this particular experiment was never detailed in full in a grant proposal).

Rahman's group concentrated on protein-truncating variants, because it is easier to assign pathogenicity to them than to missense variants, intronic variants, or copy-number variants. Also, protein-truncating variants can "add up" in the epidemiologic sense, and such surety is never quite attainable when dealing with missense variants.

In the analysis, one gene stood out: *PPM1D* (p53-inducible protein phosphate) outranked all the others by sheer statistical force. A *PPM1D* mutation was found in 18 of 6912 women with breast cancer, in 12 of 1121 women with ovarian cancer, but in only 1 of 5861 control subjects. And luckily, all the *PPM1D* mutations were located in a short 370 base-pair stretch of DNA. Corresponding crudely to an odds ratios of 15 for breast cancer and 60 for ovarian cancer, these *PPM1D* mutations are on par with *BRCA1* and *BRCA2* in terms of lifetime risk, albeit 10 times more rare.

What surprised everyone was that the *PPM1D* mutations were mosaic—that is, they appeared to arise early during development as a result of a somatic mutation, and not all cells contained the mutation. It was estimated that 15% of lymphocytes (the source of host DNA) were mutation-positive and that 85% were fine. And none of the cancer cells carried the mutation.

It is safe to assume that the *Nature* staff and reviewers were diligent in ruling out an artefactual explanation, and readers are therefore free to explore the implications of this implausible finding presuming it to be true. Investigators with similar numbers of DNA specimens collected from past patients will no doubt replicate this study shortly, alone or in consortium.

First, from a clinical point of view, the risk for ovarian cancer with *PPM1D* mutation (although not precisely known) looks to be as high as that determined for any risk factor or gene mutation yet discovered. The lifetime risk for a mutation carrier exceeds 60%, and so a preventive oophorectomy is in order. The *PPM1D* gene appears to be responsible for about 1% of ovarian cancers—fewer than *BRCA1* or *BRCA2,* but comparable to the mismatch repair genes, *RAD51C* and *RAD51D*. The clinical scenario is much different, however.

For traditional counselling in the context of traditional susceptibility genes, women can be selected for genotyping based on personal and family history, and if a mutation is found, testing can be offered to at-risk relatives. If testing shows positivity, preventive surgery is offered. In the case of *PPM1D*, because the mutations are believed to arise post-meiosis, they do not segregate within families and do not imply a recurrence risk. That is, there should be no risk increase for daughters of carriers. It is theoretically possible that the ovaries of mutation carriers contain a proportion of mutant oocytes and that they could carry a mutant allele to a daughter; however, that scenario is improbable, given that all the *PPM1D* carriers in

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the Rahman article were mosaic. Perhaps a state of 100% mutation is not viable for a fetus. Also, if each carrier represents a *de novo* somatic event, we should expect the prevalence of mutations to be roughly the same (that is, very rare) in all ethnic groups.

So, is it helpful to add *PPM1D* to the growing panel of ovarian cancer susceptibility genes?

If all healthy *PPM1D* carriers in the population were to be found, with preventive surgery offered to carriers, the number of ovarian cancers could be cut by 1%. But to reach that goal, all women in the population would have to be screened. And if all women in the population were to be screened for *PPM1D*, I suppose that they might as well be screened for *BRCA1* and *BRCA2* mutations as well. Actually, such screening might not be such a bad idea; that approach was tried in the Jewish community in Ontario with a modicum of success[2]. Should the cost of testing decline to $100 per patient, mass screening might well be cost-beneficial.

Of course the foregoing speculation is based on a single study that will no doubt be replicated or refuted in 2013. Many researchers have next-generation sequencing machines, and a few of us have grants. If this phenomenon is a general one by which cancer genes cause cancer, then other, more interesting, genes are sure to be discovered.

The Rahman group do not have a ready explanation concerning why a gene mutation present only in a fraction of lymphocytes and immeasurable in cancer cells should cause either breast or ovarian cancer. We will soon learn which other tissues are mosaic for mutations and which other cancer sites are involved. We may learn how abnormal lymphocytes stimulate cancers in other organs. Prevention remains a way off, but these few white blood cells seem a tempting target.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

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