I was diagnosed with breast cancer. How genetic testing guided what to do next.

Two months ago, I joined a club nobody wants to be a member of – the 1 in 8 women who develop breast cancer at some point in their lifetimes. It turned up on a routine mammogram.

I'm happy it's okay these days to talk about breast cancer – when my mom first had it in 1988, that wasn't true. I haven't thought much yet about marching and holding a sign next October for Breast Cancer Awareness Month. I don't have the strength to hold up a sign right now, but I'm trying to help by explaining things on the Facebook groups of "pink sisters" I've joined recently. Many of their questions concern genetic testing.

The media tends to focus on celebrities like Angelina Jolie undergoing surgery *before* they have cancer because they've inherited a susceptibility mutation. But genetic testing is also critically important for those of us who have *already* been diagnosed.

Beyond *BRCA*

After my biopsy confirmed that I had ductal carcinoma *in situ* (DCIS) – a milk duct filled with cancer cells – I knew I needed genetic testing to tell whether I needed a single or double mastectomy. As a genetic counselor, I'd never sent myself for *BRCA* testing because my family history didn't fit the classic profile of several young affected family members. Only my mom had it, and she was older. The guidelines now advise testing for anyone of Ashkenazi heritage.

Next up in this unexpected journey: choosing and meeting my breast surgeon. Before she could say much, I began babbling gene names: *BRCA*, but also C*HK2, ATM, RB1, p53, BARD1*. Several dozen genes disrupt natural DNA repair, allowing mutations in oncogenes and tumor suppressor genes to persist. A mutation in any one of them would mean both breasts had to go. I didn't want to take the risk that cancer would develop in the healthy one and I'd need a second surgery.

As my anxiety escalated, the doc spoke up.

"Ricki. You can't diagnose yourself. Find another genetic counselor."

So I did. Bonnie Liebers runs Genetic Counseling Services.com, providing telecounseling and helping patients and their health care providers access the best tests for them. The clock was ticking because my husband Larry and I were about to leave on a trip to Costa Rica planned a year ago. Genetic testing would inform my treatment and also reveal whether my three daughters and my sister needed testing too.

The next day, still stunned, I sat down with Bonnie, a personal friend. She calmly laid out the brochures from six genetic testing labs, comparing the offerings and coverage as if we were ordering takeout. We selected Invitae's 80-gene panel, a blood test. I'd hear about the most likely suspects first, such as the *BRCA* genes.

(Things are ramping up fast in the genetics of cancer diagnosis and treatment. My 2015 Angelina Jolie post mentioned Invitae's test, which then covered 34 genes. And Memorial Sloan Kettering Cancer Center recently announced a 468-gene panel for cancer cells. And that's just mutations. Gene expression profiling for predicting recurrence is another story.)

A week later, right after we'd traversed the hanging bridges through the cloud forest near the Mount Arenal volcano in Costa Rica and were waiting for our group to catch up, a magical moment of wi-fi revealed my preliminary genetic test results. No mutations in the top tier of genes! A day later another blip of connectivity in the rainforest brought news that I didn't have mutations in any of the other genes either.

Great news! So I faced a trio of time-based consequences:

Immediate: I'd only need a single mastectomy.

Short term: my daughters and sister were not at elevated risk of having inherited a susceptibility mutation in the genes I was tested for.

Long term: I could now focus on controllable risk factors. Let me explain.

Most cancers are not inherited

The public service announcement for breast cancer screening in New York state (Get Screened, No Excuses), featuring a patient proclaiming "but there's no cancer in my family," corrects the common misconception that cancer is inherited. It's most often a *genetic* disease, but not an *inherited* one. There's a difference.

In most breast cancer cases, the mutations are somatic, occurring only in the breast cells and therefore not inherited. The explanation goes back decades to the 2-hit hypothesis of cancer: Most cancers arise from two recessive mutations, or "hits," in a single body (somatic) cell.

Only 5 to 10 percent of cancers are inherited, with a mutation coming in with the sperm or egg. People who inherit cancer-susceptibility mutations, like Angelina Jolie, present in all of their cells, are already halfway to cancer at conception. All they need is one mutation in a body cell to start the disease, and that's why some elect prophylactic surgery.

My cancer was not inherited. Instead, it began when a gene whose protein product regulates the cell cycle (frequency of division) in a single cell within a single milk duct mutated. That first glitch was recessive – the normal gene counterpart on the second copy of whatever chromosome it was part of maintained the normal cell cycle. Maybe I was 7 when that initial hit happened, or 27, or 47. Who knows.

cancer 1 14 18 3

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A breast cancer cell (NHGRI).

But sometime within the past few years, in that very same cell, a second mutation zapped that very same gene, but in the second copy of the chromosome. Having two mutations in the same gene lifted the protection of recessiveness, and that cell now had an advantage: it could divide more frequently than the cells around it.

The cell may have had an advantage, but I didn't.

Soon the cancer cell divided. Then there were 2, then 4, then 8 cells, and on and on until a little lump jutted from the inner lining of a lone milk duct. The runaway cells had filled the little tube by the time I saw the "suspicious" mammogram mid-November 2017, sparkling with a trail of telltale calcifications bisecting my breast. The sparkles hadn't been there a year earlier; it was a high-grade growth.

Analyzing my controllable risk factors

Some risk factors are out of our control: being female, menstruating young and/or entering menopause late, being older, inheriting mutations. Learning that I hadn't inherited the most common breast cancer gene variants enabled me to focus on controllable risk factors. But there was one more uncontrollable circumstance to consider that's rarely written about: spontaneous mutations.

These just happen, due to a chemical phenomenon (a tautomeric shift) in which any of the four types of DNA bases – A, T, C, and G – are fleetingly in a slightly different form that has to do with the position of hydrogen bonds. If a fork of replicating DNA comes along as a base is caught in this rare form – a little like catching an executive in her jammies – then the rare base can't pair with its usual partner (A with T and G with C), and an incorrect DNA base pair is inserted. If the change to the encoded protein affects how it controls the cell cycle, cancer can result.

Spontaneous mutations are a fact of life, a consequence of chemistry. But environmental exposures can

also trigger mutations, and these are likely behind many “2-hit” cancers.

The first cancer-environment link came from British physician Sir Percival Pott, who in 1770 attributed the high rate of scrotal skin cancer among chimney sweeps in London to their crotch-level exposure to a chemical in soot.

My family is riddled with cancers, but they all began later in life and had environmental explanations – lung and tongue cancers among smokers, lymphoma in a radiologist, skin cancer in a sun worshipper. I suspect that the thyroid cancer I had in 1993 was due to 5 years of orthodontia as a kid, unprotected from the x-rays. My exposure *in utero* to diethylstilbestrol (DES) upped my breast cancer risk. Pesticides that are estrogen mimics, such as DDT, cause breast cancer too.

I’ve done what I could to lower my risk – nursed 3 babies; exercised every day; avoided cigarettes, alcohol, or estrogen patches or pills; no long-term oral contraceptives; and I spread compost and manure on my garden, not organophosphate pesticides.

But diet is something else I can control and haven’t (other than low-carb), and it ties in with my recent visit to Costa Rica.

No more beef!

Clearing land to raise cattle is destroying rainforests, as bovine flatulence pours out the greenhouse gas methane. And beef consumption has long been associated with increased cancer risk.

Grilled beef releases heterocyclic aromatic amines (HAAs), which are absorbed into the bloodstream and sent to the liver, where they’re metabolized into mutagens – chemical compounds that raise the risk of certain cancers. Broccoli and Brussels sprouts produce glucosinolates, which activate xenobiotic metabolizing enzymes that take those nasty HAAs down a different, non-mutagenic pathway.

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Spewing HAAs on the barbie isn’t the only risk of eating red meat. Absence of an enzyme makes the human immune system react to eating meat from organisms that do make the enzyme. And cattle and pigs make it.

Specifically, the enzyme, CMAH, encodes a cell surface sugar, Neu5Gc, a type of sialic acid. That sugar

functions as a “xenoantigen” – when we encounter it, our immune systems crank out antibodies and promote inflammation, raising the risk of arthritis and cancer.

Last month David Alvarez-Ponce’s team at the University of Nevada described, in Genome Biology and Evolution, how muscle tissue (aka meat) safe for human consumption is in birds, reptiles, platypuses, spiny anteaters, and of course other primates. Interestingly, some breeds of dogs and cats make the offending sialic acid and some don’t – but I don’t think anyone is contemplating consuming their pets.

Surviving cancer is all about accepting what is, yet becoming empowered to live with what is while continuing to do whatever possible to lower risks. They persist. Treated cancers can return and new ones appear. Just do the math.

We have 30 trillion cells, all but the red blood cells harboring genomes where the mutation rate is 5 in 100,000 DNA bases per cell division for the youngest, rising to 5 in 20,000 among the oldest. At last count, at least 130 of those genes are oncogenes or tumor suppressor genes. That means that being “cancer-free” is probably impossible, for any of us, and that’s why “no evidence of disease” is a more honest way for oncologists to give good news to patients.

My journey from breast cancer to genetic testing to eliminating beef may have been circuitous, but it may lower the risk of my having to go through surgery again. I wish I’d started sooner, and I hope that this post helps folks.

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