

Is cancer really just “bad luck”?

Keith Block, MD

A new paper in the premiere journal Science, by Cristian Tomasetti and Bert Vogelstein, two researchers at Johns Hopkins University, has started a hot controversy in the media. The paper claims that “bad luck,” in the form of mutations that happen randomly in the course of normal cell division, is the cause of about 2/3 of cancers. Because these mutations are not controllable, we should, therefore, de-emphasize cancer prevention efforts for these cancers in favor of screening and early detection. Many in the media, and even the authors themselves in some media interviews, are suggesting that cancer prevention efforts focused on lifestyle are essentially irrelevant. While they give lip service to the idea that some selected cancers might have a few environmental causes – smoking, for example – some of the media stories seem to suggest that it’s open season on alcohol, meat, sugar and sunbathing –and time to celebrate the news!

My analysis of several aspects of this paper is that the conclusion is so off base, it’s ludicrous. That’s not to say that there are not some interesting and valuable aspects of this paper. I am, in fact, an admirer of much of the work of Bert Vogelstein, having advocated for him as a speaker at a 2013 conference, where he gave a fascinating talk on mutations and cancer. But there are several problems with this paper and its interpretation. I’d group them as follows: technical and scientific problems with the paper itself, a failure to accurately distinguish between cancer types versus cancer cases, a lack of perspective about where mutations fit in the process of carcinogenesis, and a lack of recognition of what happens to a cancer after it is established.

The authors do some simple and elegant analyses, and come up with an interesting conclusion that answers an important question. The authors began with the question “why does cancer arise in some tissues and organs of the body more frequently than in other tissues or organs?” For instance, all the organs in the digestive system are exposed to the same mix of food and drink. So why does colon cancer occur much more frequently than small intestine cancer or esophageal cancer? Our skin is exposed to the same amount of sunshine all over. Then why is basal cell carcinoma much more common than melanoma? Tomasetti and Vogelstein answer this question with data that has only recently become available: the rate at which stem cells in different tissues and cell types in the body divide. Stem cells are the self-renewing cells that are considered the source of cancer; most of the cells in the body are already differentiated into a particular cell type and can’t become cancerous, so cancers generally arise from stem cells.

In recent years, researchers have determined that stem cells in different tissues, organs and cell types in the body divide at different rates, some more often and some less often. This is important, because each time a cell divides, there is a chance for a mutational change in the cell’s DNA that occurs randomly, not because of a carcinogenic factor. These random mutations associated with cell division are thought to be one of the causes of cancer, and the more often a stem cell type divides, the greater the likelihood of it ultimately having a cancer-causing mutation.

Although this general analysis has been known for several years, Tomasetti and Vogelstein set out to examine it more closely. They were able to obtain rates for stem cell division for 31 different types of cells, tissues or organs in the body. They then plotted the rates of stem cell division against the lifetime risk of getting cancer in each of the 31 tissue types. The resulting graph showed a very strong

correlation (a correlation coefficient of .804, to be exact). It demonstrates clearly that the more often the stem cells in a cell type, tissue or organ divide, the higher the risk of getting cancer in that tissue or organ. Basal cell carcinoma, for instance, arises in skin cells called basal cells, which are continuously dividing skin stem cells. It has the highest rate of stem cell division of the 31 types, and the highest rate of cancer incidence in the US population. Melanoma, on the other hand, arises in skin cells called melanocytes. Their rate of cell division is about 10 times less than basal cells. The risk of getting melanoma is markedly less than that of basal cell carcinoma – 76,000 versus 2.8 million cases per year in the US (www.skincancer.org). Pelvic bone cancer (osteosarcoma), arising in bones of the pelvis, has the slowest rate of cell division of the 31, and the lowest rate of cancer (about 50 cases a year). This strong correlation certainly supports the idea that rates of stem cell divisions play a significant role in the development of cancer.

However, the graph doesn't entirely overlook the influence of other factors that can cause cancer. In some cases, the authors show separate values where there are known carcinogens. For example, they show two risk levels for lung cancer – a higher one for smokers and lower one for non-smokers. We know that male smokers get cancer 23 times as often than non-smokers, and female smokers 13 times more often than non-smokers (www.cancer.org). They also show different rates for cancers known to be linked to genetic syndromes versus those not influenced by genetics; i.e., non-genetic colon cancer, and liver cancers caused by viruses versus non-viral liver cancer. To account for the effect of these lifestyle, genetic and infectious causes of cancer, they calculate what they call an "extra risk score" – multiplying the actual cancer risk in the US population by the rate of stem cell division. The extra risk score is supposed to show how much of the risk of a certain type of cancer is due to lifestyle, genetics and infection versus due to stem cell division. The extra risk scores ranged from about -18 (minimal extra risk above stem cell division) to +18 (maximum extra risk). The lowest extra risk score was for pancreatic islet cancer – the rare kind of pancreatic cancer that Steven Jobs had, not the more common pancreatic duct cancer. The highest extra risk score was for a genetically related type of colon cancer. Tomasetti and Vogelstein lined these up from lowest to highest. They then selected all the cancers with extra risk scores greater than 0 (zero) – a sensible mathematical way to divide a group up into two subgroups. Of the 31 tissue types, 9, or about 1/3, had scores greater than 0. These 9 cancers included thyroid cancer, colon and rectal cancers (both genetic and non-genetic), basal cell cancer, virally-caused liver cancer, virally-caused head and neck cancers, and lung cancer in smokers. These cancers, they concluded, were the ones that had extra cancer risk. The other 2/3 of cancers were caused by their stem cell division rate. This is where the "2/3" figure that we've been reading about comes from. Unfortunately, it's been inaccurately used in the context of "2/3 of cancers are caused by bad luck." This is simply not true.

I don't have a problem with the statistical analysis itself. It shows a quite reasonable explanation of why some tissues and organs get more cancer than others – why, for instance, colon cancer is more common than esophageal cancer, or basal cell cancer is more common than melanoma. And it establishes that yes, there *are* cancers that don't have strong lifestyle or environmental components. Many of these are cancers often found in children and young people; for example, bone cancer, or ovarian germ cell tumors, which are different from the more common ovarian carcinoma that is diagnosed in older women. They are also generally considered to be "rare" cancers.

These are my concerns. To begin with, the 31 cancers in this analysis do not include some very common cancers: breast, prostate, stomach, bladder or ovarian adenocarcinoma cancers, simply because we do not have accurate data on the stem cell division rates in these cancers. The "bad luck"

cancers include a disproportionate number of rare cancers. It is true that 2/3 of the 31 cancer types Tomasetti and Vogelstein looked at are what they described as “low extra risk,” and “bad luck” may very well be a contributing factor in their onset. But it is absolutely not accurate to say that 2/3 of **all** cancer cases in the US population are due to “bad luck.” Yet, this is the most often-repeated conclusion of the media coverage of this paper. Again, some of the most commonly diagnosed cancers are completely left out of this analysis, and, very importantly, many of these specific cancers are the very ones whose onset is linked to lifestyle and diet. According to the World Cancer Research Foundation’s most recent report, breast cancer risk is known to be increased by alcohol consumption, timing of starting menstruation and pregnancy, hormone replacement therapy, body fat, low physical activity, and lack of breastfeeding. The risk of stomach cancer is increased by bacterial infection, salted foods and smoked, grilled and barbequed meats. Bladder cancer risk is increased by tobacco use and workplace toxins. Therefore, saying that 2/3 of the people with cancer could not have avoided it by a more careful lifestyle is completely inaccurate. Fortunately, this point has been stressed by some of the more responsible media outlets covering this issue.

I have another problem with the analysis, which I have not seen raised in any other discussions of this article. Tomasetti and Vogelstein choose 0 (zero) as their cutoff for “high extra risk score.” While this makes mathematical sense, I don’t think it makes much biological sense, given what we know about some of the cancers at the high end of the “low extra risk scores.” These include esophageal cancer (score of -6), pancreatic ductal cancer (-3), gallbladder (-1.7), melanoma (-1.6) and head and neck cancer (-1). All of these are known to be heavily influenced by lifestyle or environmental factors. With esophageal cancer, alcohol use and excess body weight increase risk, especially if alcohol is accompanied by tobacco use. For pancreatic ductal cancer (the common type of pancreatic cancer), 25% of cases are caused by tobacco, and more are caused by excess body weight, especially abdominal fat. For gallbladder cancer, a major risk factor is gallstones, which we know are linked to diet. With melanoma, sun exposure, especially repeated sunburns in fair-skinned people, is a strong risk factor. And for head and neck cancers, alcohol and tobacco use are well-known risk factors. I think Tomasetti and Vogelstein should have set their “high extra risk score” at a value less than zero, based on the known biology of these cancers. There’s no real reason to use a mathematical basis instead of a biological basis in this kind of analysis.

So these points take care of my technical concerns about the paper, as well as my caution about confusing cancer *types* with cancer *cases*. What about the issue of the role of mutation in the process of carcinogenesis? Mutation is just the first step of 3 stages of formation of a clinically detectable cancer. Mutations result from the random processes involved in stem cell division, but are also known to result from free radical damage to DNA, owing to factors such as smoking and tissue inflammation. But after mutation, other processes encourage the growth of tumors in the stages called promotion and progression, which allow the cancer to become established and grow, overcoming surveillance by the immune system. Inflammation, for instance, is well known to promote the growth of tumors after they become established. This is why chronic inflammation, such as that resulting from obesity, plays a role in many types of cancers. The processes of tumor promotion and tumor progression are completely absent in the analysis of Tomasetti and Vogelstein – but they are very relevant for people who are trying to prevent cancer.

And what about processes that happen after cancer become established? If you accept the “random bad luck” theory as the explanation for your diagnosis, it would be easy to assume that the outcome of

your treatment is also completely out of your control, and that there's nothing you can do to positively influence your outcome. This is NOT a good plan. Maybe there *was* an element of "bad luck" due to the vagaries of stem cell mutation that explains why you got colon cancer and your sister, who was brought up pretty much the same way you were, did not. If so, let that serve as a good reason to not berate yourself for having gotten cancer in the first place! But that doesn't mean you should overlook the strong scientific evidence that continues to grow and demonstrate just how important it is for cancer patients to maintain an excellent diet, use supplements when needed to correct and balance their biochemical terrain, keep physically active, and regulate their biology through behavioral strategies such as stress reduction and good sleeping habits. This holds true even if your cancer is one of the rare types that does not seem to be largely influenced by environmental and lifestyle factors. For example, chronic lymphocytic leukemia (CLL) is one of the "bad luck" cancers. Yet we have a patient who was diagnosed with CLL 24 years ago. He is now in remission, and has achieved long-term control of his CLL using diet and lifestyle interventions, and an individualized supplement regimen based on both his biochemical terrain and the latest research on herbs and CLL. And this is just one patient example of many.

In conclusion, please don't let this interesting, but very limited statistical analysis mislead you into thinking that the diagnosis of a cancer that is less influenced by environmental and lifestyle factors – a "bad luck" cancer – equates with being powerless to influence the outcome of your treatment. Take a broader perspective and look at all of the science. This will help you understand the true potential of not only a healthful lifestyle, but a comprehensive, individually tailored and integrative approach to treating your disease.