DNA is so unstable that scientists estimate there are more than 20,000 DNA lesions per cell each day. The body’s base excision repair system (BER) stays busy removing these lesions and mending DNA. But sometimes the repair system is imperfect and lesions go unfixed. This defective DNA can cause cellular mutations that result in cancer.

Joann Balazs Sweasy, PhD, Professor of Therapeutic Radiology and of Genetics, studies DNA repair genes. She has recently reported two exciting findings. She and her colleagues searched databases from the National Institutes of Health, looking for DNA repair genes that might be mutated in the germline. They typed 2,700 individuals and found two coding variants that might result in altered proteins that could cause mutations.

Dr. Sweasy began the first-ever study of one of these variants, polymerase beta (Pol ß). When BER is functioning correctly, it excises the DNA lesion and then fills in the gap with a DNA polymerase. Dr. Sweasy discovered that Pol ß works more slowly than a normal polymerase and doesn’t fill in all the gaps, which accumulate. “That leads to double-strand breaks, chromosomal aberrations, and massive genomic instability,” said Dr. Sweasy.

The discovery is important, she added, because it suggests that people who carry this Pol ß variant—about three percent of the world’s population, mostly Eastern Europeans—could be at increased risk for cancer. If the Pol ß population were identified, doctors could do early monitoring for cancer. These people also might be candidates for studying the role of anti-oxidants, since reactive oxygen is linked to DNA base damage.

At the moment, it’s unknown what types of cancer Pol ß might be related to. One small experiment reported that heterozygotes with the variant who were treated for lung cancer did much worse than everybody else. Dr. Sweasy found a possible link to increased risk for breast cancer. When she put Pol ß into healthy breast cells in her lab, the variant resulted in “an extremely robust cancer phenotype.” In the cells, her Dr. Sweasy married to create people with breast cancer as if they carry Pol ß. “We would like to try ordering in different ‘cancer populations’,” said Dr. Sweasy.

Dr. Sweasy’s second finding is drawn from the databases and relates to an enzyme called glycosylase, which cuts out damaged bases from DNA. She discovered that about 10 percent of the population—a significant number—have a variant in the germline. When Dr. Sweasy expressed this variant in different kinds of cells, they became extremely sensitive to 5-fluorouracil (5-FU), an inexpensive drug used to treat a variety of cancers, including breast, pancreatic, and colon.

“The question we’re really asking is which mutations are actually associated with cancer risk and which can possibly cripple the repair system.”

So right off the top, said Dr. Sweasy, “we can say that if somebody reports over to Smilow with breast or colon or pancreas cancer, and if we type them for this variant, we know their tumors would be highly sensitive to 5-FU. But even better—we’re biochemists at heart—we know how this glycosylase works, so we’re thinking about designing experiments to find molecules that might hit that specific target and give a more powerful drug than 5-FU.”

The discovery of how these two variants function in basic excision repair has wider implications. It’s likely that other repair genes have mutations. Dr. Sweasy hopes to track them. “The question we’re really asking is which mutations are actually associated with cancer risk,” she said, “and which can possibly cripple the repair system.” If we know that, patients could come in and get pre-treatment done, and then get the drugs that are most effective.”