**Fractured Sleep Exacts a Heavy Toll**

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February 19, 2014

The Many Effects of Sleep Deprivation

Hello. I'm Dr. David Johnson, Professor of Medicine and Chief of Gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia.

Recently, I discussed the implications of sleep deprivation and inflammatory bowel disease, including the upregulation of pro-inflammatory cytokines, tumor necrosis factor (TNF) alpha, and factors that mediate toward potential relapse, even in patients with remission of inflammatory bowel disease. This suggests a causal link in recalcitrant disease as well as early relapse in patients who were deemed to be in clinical remission.

I want to continue that theme with a very provocative study that was just published in Cancer Research.[1] I will get to the relationship between sleep deprivation and tumor genesis and the acceleration of cancer tumors as it relates to several different cancers in a moment, but first, let's review sleep deprivation so that you understand what the literature shows to date.

Sleep deprivation has a profound impact on multiple disease states. For example, if you sleep less than 6 hours, epidemiologic studies show the following:

• Stroke is increased by a factor of 4 times.

• Obesity is increased by an increase in ghrelin, which is a hunger hormone.

• Diabetes is increased because sleep deprivation increases insulin resistance.

• Memory loss is accelerated. Epidemiologic studies show that there is not only permanent cognitive loss but also evidence of early brain deterioration.

• Osteoporosis is increased, at least in an animal model, with changes in bone mineral density. Even changes in bone marrow are evident within 3 months of a study in a rat model.

• Cardiac disease is increased. There is a 48% increase in early cardiac death, as well as increased cardiac-related mortality.

• A 4-fold overall increase in mortality.

As it relates to gastrointestinal disease, there is an increased risk for colon cancer, and at least 1 epidemiologic study shows an association between sleep deprivation (or lack of sleep) and an increase in the likelihood of precancerous (adenomatous) polyps.

Now, let's take it a step further and look at a recent animal study published in Cancer Research.

The Toll-like Receptor 4 Pathway

The investigators used a mouse model to study a proinflammatory signaling pathway that has been linked with a variety of cancers. This toll-like receptor 4 (TLR4) pathway has been implicated in several cancers. Colon, gastric, breast, bladder, prostate, and salivary cancers have all been tied to the disruption or upregulation of the TLR4 pathway.

From some elegant work by Maria Abreu and her colleagues [2-5] at the University of Miami, we know that TLR4 is upregulated in inflammatory bowel disease-related cancers and in adenomatous polyps, the more dysplastic polyps. In fact, in colon cancer in general, TLR4 is upregulated. Why is TLR4 an important factor in these proinflammatory pathways?

TLR4 promotes the immune response, at least in the colon cancer model, by inducing immunosuppressive cytokines and apoptosis resistance. It promotes adhesion of these colon cancer cells, all of which mediate toward a more aggressive cancer as it relates to the potential for angiogenesis factors, which stimulate the TLR4 pathway as well.

Let's get to the present study. This study was looking at a group of mice that included some that were genetically engineered to be TLR4-negative. This sounds like fairly basic science, but it has profound implications. The TLR4 pathway was expressed in some of the mice, and TLR4 was genetically engineered to be negative in others.

Mice are nocturnal animals. To sleep-deprive half of the mice, the investigators put them in cages and ran a brush through the cage every 2 minutes to wake them up. The other group was allowed to sleep undisturbed. After 1 week, they injected both groups of mice with tumor cells.

All of the mice developed cancer within 9-12 days. They restudied the mice within 4 weeks. They found that in the sleep-deprived mice, the tumors were twice as large and far more invasive than they were in the sleep-undisturbed mice. The TLR4 pathway was potentially being upregulated by sleep deprivation.

In the genetically engineered TLR4-negative mice, the tumors were the same size as those in the sleep-undisturbed mice. Without TLR4, sleep deprivation had no effect on tumor growth, and the aggressive features of sleep deprivation were abolished.

Profound Implications for Sleep Health

This has profound implications for the advancement of tumorigenesis, immunosuppressive cytokines, the development of apoptosis resistance, and the promotion of cellular adhesion for the cancer cells. This may also have implications for chemotherapy, as we look at these pathways and potentially find ways to target the TLR4 signalling pathway with chemotherapy. We do know from colon cancer that patients who have early relapse also have upregulation of TLR4, so there are implications for counseling patients about sleep.

Returning to the animal model, the researchers also looked at tumor-associated macrophages (TAMs) in these cancers, of which there are 2 types: M1 and M2.

M1 is a macrophage that protects and upregulates the immune system and protects it against cancer cells. M1 was more evident in the mice that had normal sleep, and it was markedly reduced in the sleep-deprived mice.

The opposite was true for M2, which is a deleterious cell that promotes angiogenesis and inhibits the immune system. As you might expect, in these sleep-deprived mice, M2 was increased, and decreased in the mice with normal sleep.

So let's put it all together. Sleep deprivation, or fragmentation, has profound implications for cancer biology. From a gastroenterology standpoint, it has profound implications, because it may be related to colon cancer and gastric cancer and is certainly in the pathway to chronic bowel disease and its progression to cancer genesis.

Where this plays out with respect to the activity of inflammatory bowel disease, I can't speak to at this point. However, the implications for cancer are fairly profound. We talked earlier about sleep and the implications for multiple disease states -- virtually all of the systems of the body are affected.

It's time that we start talking to our patients about this. Patients who are sick need to hear this more clearly, and for prevention, we can perhaps do more proactively to reduce the risk for cancer. Instead of looking at sleep and saying, "I only slept 3 hours last night," as a macho thing, it's time to say, "How dare you harm yourself. You can do better."

We need to open up our eyes to the value of closing them. Take the time to talk to your patients about what you do. We are probably the most sleep-deprived group of people that we know, but nonetheless, we need to do a better job in the education of our patients.

References

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