Fragmented Sleep Accelerates Cancer Growth

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Poor-quality sleep marked by frequent awakenings can speed cancer growth, increase tumor aggressiveness and dampen the immune system's ability to control or eradicate early cancers, according to a new study published online January 21, 2014, in the journalCancer Research.

The study is the first to demonstrate, in an animal model, the direct effects of fragmented sleep on tumor growth and invasiveness, and it points to a biological mechanism that could serve as a potential target for therapy.

"It's not the tumor, it's the immune system," said study director David Gozal, MD, chairman of pediatrics at the University of Chicago Comer Children's Hospital. "Fragmented sleep changes how the immune system deals with cancer in ways that make the disease more aggressive."

"Fortunately, our study also points to a potential drug target," he said. "Toll-like receptor 4, a biological messenger, helps control activation of the innate immune system. It appears to be a lynchpin for the cancer-promoting effects of sleep loss. The effects of fragmented sleep that we focused on were not seen in mice that lacked this protein."

Gozal, an authority on the consequences of sleep apnea, was struck by two recent studies linking apnea to increased cancer mortality. So he and colleagues from the University of Chicago and the University of Louisville devised a series of experiments to measure the effects of disrupted sleep on cancer.

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The immune systems of mice that slept undisturbed were better able to inhibit cancer growth.

Study with Mice

They used mice, housed in small groups. During the day—when mice normally sleep—a quiet, motorized brush moved through half of the cages every two minutes, forcing those mice to wake up and then go back to sleep. The rest of the mice were not disturbed.

After seven days in this setting, both groups of mice were injected with cells from one of two tumor types (TC-1 or 3LLC). All mice developed palpable tumors within 9 to 12 days. Four weeks after inoculation the researchers evaluated the tumors.

They found that tumors from mice with fragmented sleep were twice as large, for both tumor types, as those from mice that had slept normally. A follow-up experiment found that when tumor cells were implanted in the thigh muscle, which should help contain growth, the tumors were much more aggressive and invaded surrounding tissues in mice with disrupted sleep.

"In that setting, tumors are usually encased by a capsule of surrounding tissue, like a scar," Gozal said. "They form little spheres, with nice demarcation between cancerous and normal tissue. But in the fragmented-sleep mice, the tumors were much more invasive. They pushed through the capsule. They went into the muscle, into the bone. It was a mess."

Immune System Cancer Response

The difference appeared to be driven by cells from the immune system, called tumor-a ssociated macrophages (TAMs), which cluster at the site of tumors. TAMs are a hallmark of the immune system's response to cancer, but they can respond in a variety of ways, depending on chemical signals they receive. Some, labeled M1, promote a strong immune response and can eliminate tumors cells. Others, known as M2, suppress the immune response and instead promote the growth of new blood vessels—which encourages tumor growth.

Well-rested mice had primarily M1-type TAMs, concentrated in the core of the tumors. Sleep-fragmented mice had primarily M2-type TAMs. These were abundant, especially around the periphery of the tumors. The sleep-disrupted mice also had high levels of toll-like receptor 4 (TLR4).

Key Proteins

Three key molecules are part of the signaling pathway that appeared to be tilting macrophages toward M2: TLR4 and two downstream signals called MYD88 and TRIF.

So the researchers injected tumor cells into a series of mice that were unable to produce one of these three proteins and subjected them to fragmented sleep. Tumor growth was slightly reduced in mice lacking MYD88 or TRIF, but in mice lacking TLR4, tumor growth was no greater than in mice with undisturbed sleep.

Taking TLR4 out of the picture resulted in major curtailment of tumor growth. "When we injected tumor cells into mice that lacked TLR4," Gozal said, "the differences between undisturbed and sleep-fragmented mice disappeared."

"This study offers biological plausibility to the epidemiological associations between perturbed sleep and cancer outcomes," Gozal said. "The take home message is to take care of your sleep quality and quantity like you take care of your bank account."

The Centers for Disease Control and Prevention estimate that about 70 million Americans suffer from chronic sleep problems. "Considering the high prevalence of both sleep disorders and cancer in middle age or older populations," the authors wrote, "there are far-reaching implications." Their next step is to determine whether sleep affects metastasis or resistance to cancer chemotherapy.

The National Institutes of Health funded this study.

From Newswise

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Circadian rhythms tell humans and animals when it's time to sleep and wake. Irregular sleep patterns disrupt the intricate chemical network of hormones that start preparing the body for sleep hours before bedtime.

Insomnia: The Role of Sleep

PART 2

By Ronald D. Whitmont

Sleep was once thought to be a relatively passive process of decreased brain activity. More-recent data indicates that sleep, like consciousness, is an active process characterized by a myriad of complex electrical and neuroendocrine brain activities.

The benefits of healthy sleep are profound as are the drawbacks of deprivation. Every system of the body is affected by sleep, including physical, emotional, and cognitive functioning. Sleep promotes healing and recovery from illness, improved stamina, and the ability to learn and remember new skills.

Healthy sleep usually includes dreaming (even when it isn't remembered), which also appears to play a powerful role in psychological and emotional health, memory, and the ability to learn new tasks.

Sleep Medications

Healthy sleep is still somewhat of a mystery since it is only partially understood and has never been artificially duplicated. While medications mimic the appearance of sleep, they do not reproduce the quality or restorative, integrative functions of sleep.

In most cases, medications used to promote sleep eventually backfire and erode it, making the condition dependent on escalating doses of drugs and more resistant to treatment.

Sleep Deprivation

Deep sleep has anti-inflammatory benefits. It helps restore hormonal balances, provides rest, and clears the mind like rebooting a computer.

Sleep deprivation causes significant physical and emotional effects, including changes in cardiovascular function, glucose metabolism, insulin resistance, and elevations of blood pressure, blood sugar, and cortisol.

Long-term effects of deprivation are linked to increased risk of developing many chronic diseases, including cancer, premature aging, depression, and gastrointestinal disorders.

Sleep deprivation is an effective method of persuasion, with a history of use in times of war and in indoctrination programs, including military and medical-residency training. Deprivation affects sanity, impairs vigilance, and erodes physical endurance.

Deprivation makes for more-compliant subjects who think less, concentrate poorly, and rely on automatic behaviors. Deprivation alters brain chemistry and interferes with a sense of reality, eventually disturbing mental and emotional stability.

Chronic Insomnia

Passage into sleep requires a gentle lapse of consciousness and awareness, coinciding with internal and external environmental supports to sustain it. In cases of chronic insomnia, the body actually loses its innate ability to relax, and lapse into and sustain healthy sleep.

Sleep is an unconscious process that relies on an elegant network of biologic, chemical, hormonal, and neuroendocrine pathways collectively working together as biorhythms or circadian rhythms. When these circadian rhythms are allowed to function unhindered, they reproduce the same biochemical patterns on a daily basis.

The body relies on this system like an internal clock to efficiently manage the sleep-wake cycle. Unless it is tampered or interfered with, these internal rhythms help maintain a healthy mental, physical, and emotional balance through sleep.

When the circadian pattern is regular and uninterrupted, day after day, week after week, and year after year, the physical and emotional body learns to anticipate and depend on the pattern, preparing for these cycles many hours in advance.

Breaking the biorhythm in an irregular or unpredictable manner disrupts the intricate chemical network of hormones and neurotransmitters and forces the body to readapt, sometimes in midstream.

The body adjusts readily enough in youth, but as it ages, it is less able to change as quickly. Sometimes even simple changes in routine can lead to large disruptions in sleep and wakefulness. This is one reason why advancing age is associated with a greater number of sleep disturbances.

Causes of Insomnia

When insomnia first strikes, its roots are frequently traceable to one or more well-defined disturbances of medical, chemical, dietary, environmental, emotional, or behavioral causes that will be described in a subsequent article. These causes frequently combine in a complex web of interaction that can be remedied by utilizing simple sleep-hygiene techniques coupled with carefully selected classical homeopathic medicines.

This is the second part of a 10-part series. Next week: Sleep hygiene and treatment of sleep disorders.

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