Difficulty sleeping and disturbed sleep patterns are not uncommon among cancer patients, and alleviating these symptoms has always been integral to good cancer care. Now, mounting evidence of the impact that getting enough deep sleep can have on outcomes in some cancers makes it even more important for patients to be given the sleep support they need, write Adriana and Francesca Albini.

Despite centuries of wisdom recognising the importance of sleep, modern society has relegated it to a secondary concern, often sacrificed to work demands, entertainment and the distractions of modern technology. Busyness has become a badge of honour, with public figures often boasting about surviving, thriving even, on just five hours per night. With its demand for stillness and surrender, sleep feels almost subversive in a culture obsessed with constant activity.

Yet growing evidence indicates that a good night's sleep is more than just a lifestyle preference, and that it plays a crucial role in promoting and maintaining our health. Research has consistently shown that the quality and duration of sleep impacts on our risk of developing many chronic conditions, such as obesity, diabetes, depression, high blood pressure, stroke, and heart disease. Evidence for an impact on the risk of many types of cancer has also been steadily growing, supported by both epidemiological and experimental studies. While much remains uncertain or poorly understood, the case is building for advice and support on sleep to be added to diet and exercise to help people lower their risk of cancer.

Evidence from epidemiology

Epidemiological studies using various methodologies are throwing a light on the link between various sleep characteristics and different types of cancer. Not all findings are consistent, and more evidence will be needed to understand the complexities and possible confounders.

Colorectal cancer

Certain sleep disorders <u>raise the risk of colorectal cancer (CRC)</u> by more than 50%, according a case-control study by Lin et al. (adjusted odds ratio 1.76 for sleep apnoea, 1.54 for insomnia, and 1.29 for any sleep disorder).

Both short and long sleep durations have been identified as risk factors. Research by Zhang et al., at Brigham and Women's Hospital and Harvard Medical School, in Boston, linked <u>sleeping 9+ hours</u> to higher risk of colorectal cancer, particularly among overweight individuals or those who snored. Thompson and her group at Case Western Reserve University, Cleveland, Ohio, <u>found short sleep</u> duration increased colorectal adenoma risk.

A randomised study found that <u>snoring was associated with higher rectal and colon cancer risk</u>. Difficulty sleeping or frequent awakenings have also been linked to colorectal cancer, with UK Biobank data suggesting <u>that good sleep quality might serve as a protective factor</u>. A Mendelian randomisation study which will soon be published in *Frontiers in Oncology* suggests that <u>an</u> <u>individual's chronotype</u> – their preferred sleeping and waking periods over 24 hours – influences their risk of developing CRC. The authors advise that adopting healthier sleep patterns could serve as a preventive measure to reduce this risk .

Prostate cancer

The relationship between sleep disturbance and prostate cancer risk remains complex, with studies producing mixed and often contradictory results.

An American Cancer Society study by Gapstur et al. found a <u>higher risk of fatal prostate cancer</u> <u>associated with short sleep duration</u> during the first eight years of follow-up. The REDUCE trial identified <u>elevated odds of high-grade prostate cancer in men who reported trouble falling asleep</u>. Additionally, research based on actigraphy (which measures body movement over time) revealed that men experiencing <u>prolonged wakefulness after sleep onset had an increased risk of prostate cancer</u>.

<u>Chronotype seems to exert an influence</u>, whereby evening types may be more susceptible to the negative effects of sleep deprivation on prostate cancer risk. However, several studies found no consistent link between sleep patterns and prostate cancer risk. The Health Professionals Follow-Up Study, for instance, reported <u>no association between sleep duration or changes in sleep duration and advanced or lethal prostate cancer</u>.

Lung cancer

<u>Short sleep duration</u> was associated with a 13% increased lung cancer risk in a 2023 meta-analysis, while <u>long sleep duration</u> (>8 hours) was linked to increased risk in a large 2022 UK study, which also concluded that frequent insomnia symptoms, and a pronounced evening chronotype, may contribute to an increased risk of lung cancer.

Ovarian cancer

Sleep patterns, particularly the presence of sleep disorders like insomnia, have been increasingly linked to the risk and prognosis of ovarian cancer.

A large-scale population-based cohort study conducted by Wu Zheng et al., employing propensity score matching, demonstrated that people with sleep disorders had a <u>significantly higher risk of</u> <u>developing ovarian cancer</u>, with an adjusted incidence rate ratio of 1.30 compared to those without such disorders.

A Mendelian randomisation study found that <u>insomnia was associated with a 60% increased risk</u> of endometrioid epithelial ovarian cancer, with an odds ratio of 1.60. However, conflicting evidence complicates the narrative surrounding sleep and ovarian cancer risk. For instance, a study involving over 109,000 postmenopausal women found <u>no significant overall association between sleep</u> <u>duration or quality and ovarian cancer</u> incidence. Despite this, the study noted that <u>insomnia was</u> <u>linked to an increased risk of invasive serous ovarian cancer</u>, with a hazard ratio of 1.36. Conversely, restful sleep quality was associated with reduced risks for certain cancer subtypes.

Breast cancer

The relationship between sleep and breast cancer risk has been studied extensively.

While some studies have suggested links between sleep duration and cancer incidence, the evidence remains inconsistent. A large-scale study using data from the Million Women Study <u>found no</u> <u>significant association between sleep duration and breast cancer risk</u> after adjusting for confounding factors, highlighting the need for careful interpretation of results in this field.

Sleep quality, including difficulties falling or staying asleep, has yielded mixed results regarding breast cancer risk. A 2023 case-control study in China provided compelling evidence, finding that women with short sleep durations had a significantly higher risk of breast cancer, with an odds ratio of 4.86. This study also identified specific genetic variants in the circadian genes CRY2 and PER1 linked to increased breast cancer risk, underscoring the potential role of genetic factors in the

sleep-cancer relationship.

Other cancers

Sleep disturbances are also increasingly recognised as significant risk factors for various other cancers, including oral, thyroid, and kidney.

The biology behind the link

While the epidemiological data provide strong evidence of a relationship between the duration and quality of sleep and risk of different types of cancer, unravelling the nature of that relationship is not easy. Sleep disturbances can elevate cancer risk, yet cancer itself often disrupts sleep, which can make it difficult to identify which came first.

The impact of different types of sleep disturbances and different durations differs by cancer type, as well as by age and sex. The increase in overall cancer risk associated with insomnia seems higher among younger age groups, particularly between 20 and 59.

Disruptions in circadian rhythms, alterations in immune function, and hormonal imbalances are among the biological pathways thought to mediate the connection between sleep disorders and cancer. There are also many confounding factors, which muddy the waters further; obesity, chronic inflammation, and stress, for instance, are all linked to both sleep disturbances and cancer risk. Recent research also highlights the role of genetic factors. Variants in circadian genes have been identified that may influence both sleep patterns and susceptibility to cancer, suggesting a shared genetic basis for these conditions in some individuals.

Efforts to reveal how sleep issues impact on cancer risk focus primarily on disruption of several biological systems that normally function harmoniously to maintain health.

Circadian rhythm

Disruption of the circadian rhythm is one of the most critical factors, as it interferes with the body's internal clock, which regulates DNA repair, gene expression, metabolism, and hormone production. This misalignment can lead to the accumulation of DNA damage, dysregulated cell growth, and hormonal imbalances, for instance in the stress hormone cortisol or the sex hormone oestrogen, all of which create a fertile environment for cancer development. Disruption of the circadian rhythm has been implicated in studies showing higher levels of breast cancer risk among night shift workers, though that increased risk level has not been conclusively demonstrated.

Melatonin

Production of melatonin is primarily governed by the circadian rhythm. Produced primarily at night, melatonin not only regulates sleep-wake cycles, but also serves as a potent antioxidant, protecting cells from oxidative stress and DNA damage. Melatonin's anti-proliferative properties, and its role in enhancing immune function and inhibiting tumour angiogenesis, make its reduction caused by sleep disruption a significant concern in cancer prevention.

Chronic inflammation

A well-known driver of cancer, and often associated with insulin resistance, chronic inflammation is one of the consequences of poor sleep. Good sleep upregulates anti-inflammatory cytokines, such as IL-10. Sleep disturbances elevate levels of pro-inflammatory cytokines such as IL-1, IL-6, TNF- α , and

C-reactive protein, contributing to oxidative stress, epigenetic changes, and the creation of a tumour-promoting microenvironment. These inflammatory processes can accelerate cancer initiation and progression, particularly in environments already predisposed to malignancy.

Immune system

The immune system, crucial for identifying and eliminating cancerous cells, is also impaired by inadequate sleep. Sleep deprivation weakens immunosurveillance mechanisms, reduces the activity of natural killer cells, and disrupts the balance of cytokines that regulate immune responses. These deficits undermine the body's ability to prevent or combat the development of cancer. The impact of sleep disturbances on cancer risk varies across different cancer types, with some showing stronger associations with sleep patterns than others.

Insulin

Sleep deprivation has also been shown to impair insulin sensitivity, making it harder for the body to manage blood sugar levels. Even short periods of restricted sleep can decrease glucose tolerance and increase insulin resistance. Insulin acts as a potent mitogen, stimulating cell division and proliferation. Elevated insulin levels resulting from insulin resistance can significantly impact cancer development and progression. It facilitates metabolic reprogramming in cancer cells, increasing glucose uptake and providing more fuel for growth and division. This can be particularly problematic for cancer cells expressing high levels of insulin receptors or insulin-like growth factor 1 receptors. When insulin binds to these receptors, it activates crucial signalling cascades. The growth-promoting effects of elevated insulin extend beyond tumour initiation, influencing cancer progression and metastasis by enhancing cancer cell survival, promoting angiogenesis, and facilitating cancer cell invasion.

The European Society for Medical Oncology recommends regular screening and assessment for insomnia throughout all phases of treatment and survivorship. Many comprehensive cancer centres do now have integrated sleep assessment and intervention as fundamental components of oncology care, aiming to enhance both patient wellbeing and treatment effectiveness. These centres employ integrative approaches, including cognitive behavioural therapy for insomnia (CBT-I), relaxation techniques, sleep hygiene education, and, when necessary, pharmacological interventions, to improve sleep quality in cancer patients. However, this attention to patients' sleep health is not reflected across all oncology practice. More generally, the importance of good sleep to health and the prevention of illness does not get the attention it deserves.

We live in an era of unprecedented medical and scientific advancement, yet the fundamental role of good sleep in preserving our health continues to be largely overlooked and unaddressed. Sleep, once revered as nature's healer, is now a silent casualty in the battle between modern living and human biology. The American Academy of Sleep Medicine in recent years has issued a wake-up call, declaring that "Sleep is a biological necessity, and insufficient sleep and untreated sleep disorders are detrimental for health, well-being, and public safety." It emphasised the need for a much greater focus on sleep health, alongside a healthy diet and physical activity, in education, clinical practice, public health promotion, and the workplace.

Given the potential impact of sleep on cancer outcomes, oncologists and patients alike should be made aware of the benefits of good sleep in both symptom management and potential disease progression. Measures should include routine sleep quality assessment, early intervention, and integration of sleep specialists into cancer care teams.