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Circadian disruption-induced breast cancer – knowns and unknowns

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In 2007, the International Agency for Research on Cancer stated that "shiftwork that involves circadian disruption is probably carcinogenic to humans."[1] Studies conducted before and since this claim have all provided evidence supporting the notion that circadian disruption (CD) is a warranted concern. Research has shown that CD can cause aberrant nocturnal levels of melatonin; that circadian-relevant genes are involved in breast cancer development; and that CD can cause aberrant changes in DNA methylation. Further, case study findings have provided indirect evidence that night-shift workers are at a higher risk of developing breast cancer.[2] However, despite the compounding evidence across these studies, a glaring omission is present: none of these studies provide direct, experimental evidence proving that CD promotes or increases the risk of breast cancer development. These experimental studies involved artificial levels of melatonin, chemically-induced tumors, or tumor xenografts, as well as human case studies involving many variables and inter-individual variabilities that cannot be precisely controlled and accounted for. Two recent papers, however—"Circadian disruption-induced microRNAome deregulation in rat mammary gland tissues" (by us) and "Chronically alternating light cycles increases breast cancer risk in mice"—*do* provide the necessary experimental evidence to prove that CD can directly promote and increase the risk of breast cancer development.[3,4]

Our study provides experimental evidence to prove that CD directly changes micro RNA (miRNA) expression and related proteins in mammary tissues, and that these changes display oncogenic trends related to breast cancer. Specifically, CD results in the aberrant expression of an interconnected web of miRNAs and proteins revolving around innate immunity, inflammation, and cellular senescence, all of which are crucial components in the initiation and development of breast cancer.[3] Many miRNAs with predicted circadian-relevant targets involved in breast cancer are also aberrantly expressed due to CD.[3] A study published by Van Dycke et al. also provides experimental evidence that CD increases the rate of breast tumor development in high-risk individuals, and that these changes are linked to and associated with body temperature and weight change.[4] Further, their data shows that internal desynchronization and sleep disturbance are possible mechanisms that link CD with cancer development and obesity.[4]

When taken with previous research, these recent experimental findings confirm CD as a carcinogen and a very serious concern. Statistics reveal a higher risk of breast cancer in developed countries compared to underdeveloped countries.[5] Although there are many aspects that need to be considered when explaining these statistics, such as differences in diet and lifestyle, one major contributing factor could be the increased occurrence of CD in developed countries.[5] In Canada, for example, one third of the labor force does not work a regular daytime shift; in the United States, only 25% of work is done during regular daytime employment hours (Monday to Friday).[6,7] It is also important to note that shift work is not the only cause of CD. Time zone changes, jet lag, space travel, psychiatric disorders, and even exposure to artificial light from lamps and electronics during evening hours can cause CD.[2] Given these statistics and the array of triggers that can induce CD, combined with the presented evidence and previous scientific studies, CD-induced breast cancer is a growing and serious threat that requires immediate attention.

The next steps in investigating CD-induced breast cancer should include environmentally-controlled experiments using model systems. By exposing model systems that have a genetic predisposition to cancer, such as the mouse model employed by Van Dycke et al., to varying degrees and different types of CD, researchers may reach a deeper understanding of the carcinogenicity of CD. Our results suggest that CD-induced changes in miRNA expression are likely plastic (and the degree of CD and length of re-entrainment influences this plasticity), and it is a known fact that circadian rhythms can be re-entrained; thus, an environmentally-controlled model system approach would help identify potential CD thresholds and recovery times. There is also growing evidence that epigenetics contributes to CD-induced breast cancer.[2,3] Therefore, future experiments need to investigate occurring epigenetic changes and identify how these changes influence and interact with the hormonal and metabolic changes associated with CD. By employing a variety of environmentally-controlled experiments, new insights will emerge, thus creating the possibility for new shift work policies and preventative therapies that can aid the millions of people at risk of developing CD-induced breast cancer worldwide.

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