Altered SIRT1 Activity and Plasma Cortisol as Biomarkers of Circadian Disruption in Night Shift Workers

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Disruption of circadian rhythm by persistent night-shift showed to increase the risk of breast cancer. Identification and validation of biomarkers is essential to the development of preventive strategies for individuals, especially nurses, at elevated risk of breast cancer due to shift work. Our animal studies indicate that NAD^+/NADH and SIRT1 are key regulators of circadian gene expression, which play important roles in mammary carcinogenesis associated with disruption of circadian rhythm. We used a two-phase approach to assess NAD^+/NADH and SIRT1 activity in peripheral blood mononuclear cells (PBMC) as biomarkers for circadian disruption in night-shift workers. In Phase I, we analyzed circadian rhythm of NAD^+/NADH and SIRT1 activity in day- vs night-shift workers over 24 hr; in Phase II, we assessed the same markers in another group of day- vs night-shift workers at two selected time points. In the both phases, peripheral blood was collected and PBMC were isolated from plasma. NAD^+/NADH and SIRT1 activity were analyzed in PBMC, and melatonin and cortisol were analyzed in plasma. In Phase I (n=22), SIRT1 activity differed significantly over time points across a day with an increase from early to late night in day-shift workers, while the levels were largely unchanged over time in night-shift workers. These resulted in the largest difference in SIRT1 activity at late night (midnight) between day- and night-shift workers, although no statistical significance observed. NAD^+/NADH did not have any significant differences between day- and night-shift workers, and between early and late night. In Phase II (n=39), a similar pattern was observed with a late night increase in SIRT1 activity in the day-shift but not in the night-shift workers, showing a low to moderate reliability. In addition, while the plasma melatonin did not show difference over 24 hr in day- vs night-shift workers with a peak at 4 am, night-shift dampened rhythmic secretion of cortisol over a day, resulting in significant reduction of cortisol level at morning and further misalignment of cortisol to melatonin. These preliminary results suggest that suppression of the SIRT1 activity increase at late vs early night, and suppression of early morning plasma cortisol warrant further investigation as biomarkers of circadian disruption in night-shift workers. *Supported by 1 NIH/NIEHSR21 and 1 NIH/NIEHS ES005022-27.*