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Title: Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea

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Body: Background: Obstructive sleep apnea (OSA) is associated with an increased risk of cancer mortality in humans (Nieto et al., ATS Congress, 2012). Experimental data in mice have recently shown that application of a pattern of intermittent hypoxia similar to the one observed in OSA patients enhances the rate of tumor growth (Almendros et al., Eur Respir J. 2012; 39:215-7). However, whether intermittent hypoxia mimicking OSA also increases the metastatic potential of tumors is unknown. Aim: To test the hypothesis that intermittent hypoxia enhances metastasis to the lung from a subcutaneous melanoma. Methods: 28 male C57BL/6J mice were investigated. To induce a melanoma tumor in each mouse, one million of B16F10 cells were subcutaneously injected in the left flank region of the animal. Thirteen of these animals were then subjected to breathe intermittently hypoxic air with a pattern mimicking OSA: 20 s 5% O_2 followed by 40 s room air, for 6 h/day. The other 15 animals were breathing room air (controls). After 30 days the mice were sacrificed, their lungs were excised and hematoxilyn-eosin preparations were analyzed by a pathologist to quantify the number of metastases. Results: The number of lung metastases in each mouse was significantly greater in the animals subjected to intermittent hypoxia (5.5 ± 3.2) (mean ± SE) than in control mice (1.0 ± 0.6) (p=0.028). Conclusion: The data from this animal study strongly suggest that cancer metastasis could by enhanced in patients with OSA.