## Heart-Rate Variability Moderates the Relation between Life Threatening Events and Cancer-Development: Making Cancer Less "Vague"

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Abstract : Background: Many patients and even certain clinicians attribute cancer development to psychosocial factors. Yet, empirical data supports more the prognostic role, rather than the etiological role, of psychosocial factors in cancer. Part of the inconsistency may result from not considering possible moderating factors in the etiological role of psychosocial factors. One important candidate moderating factor is the vagal nerve, whose activity is indexed by heart-rate variability (HRV). The vagal nerve may prevent cancer since it reduces inflammation on the one hand, and since it increases anti-tumor immunity on the other hand. This study examined the moderating role of the vagus in the relation between life threatening events (LTE) and cancer development. Method: We re-analyzed data from the Lifelines Dutch longitudinal cohort study of over 150,000 people. The present study included 82,751 adults, who initially were cancer-free. We extracted information on background factors (e.g., age, gender, fat consumption), whether they ever experienced LTE, HRV and cancer diagnosis as reported by patients in annual clinic visits. HRV was derived from brief ECGs. Results: Of the full sample, 1011 people developed cancer during a follow-up. In the full sample, LTE significantly predicted cancer development (R.R = 1.063 p < .01) and HRV significantly predicted a reduced risk of cancer development (R.R = .506 p <.001). Importantly, LTE significantly predicted cancer only when HRV was low (R.R = 1.056, 95% CI: 1.007 - 1.108, p < .05) but not when HRV was high (R.R = 1.014; 95% CI: 0.916 -1.122, p > 0.05), independent of confounders. Conclusions: To the best of our knowledge, this is the first study showing in a large sample that LTE predict cancer development, and that this occurs only when vagal nerve activity (HRV) is relatively low. These results could result from lack of vagal modulation of inflammation and also from lack of vagal modulation of stress responses. Results are in line with the cancer-protective role of the vagus. HRV needs to be routinely monitored in the population and future intervention trials need to examine whether vagal nerve activation can prevent cancer in people with LTE and with other cancer risk factors.

Keywords : cancer development, life-events, moderation, vagal nerve

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