



Why we Should Stimulate the Vagus Nerve in Cancer

Marijke De Couck^{1,2*} and Ralf Caers³

¹Department of Mental Health, Wellbeing Research Group, Vrije Universiteit Brussel, Belgium

²Department of Health Care, University College Odisee, Belgium

³Department of Work and Organization Studies, KU Leuven, Belgium

Abstract

Cancer-related fatigue, pain, anxiety, depression, insomnia and cognitive impairment often co-occur in metastatic cancer. Their co-occurrence can be explained by a commonetio logical factor, namely excessive inflammation, which also contributes totumorigenesis. Recent research shows that the vagus nerve has an anti-inflammatory role and has protective effects against these symptoms and prognosis in various cancers. Initially high vagus nerve activity independently predicts better cancer prognosis, specifically in the metastatic stage, and attenuates these symptoms. Various (semi) experimental studies in humans and animals showed that vagotomy accelerates tumor growth, while vagal nerve activation improves cancer prognosis. Since cancer patients also have a low vagus nerve activity, these points to strong need to activate this nerve and thereby reduce the symptom cluster and prolong survival, via the reduction of inflammation. This article reveals neuro modulation of tumors and proposes a novel adjuvant cancer therapy to improve patients' prognosis and quality of life.

Keywords: Vagus nerve stimulation; Cancer; Neuromodulation; Symptom-reduction

Symptom-Cluster

Even though treatments are improving, approximately 30% to 40% of cancer patients will develop metastatic disease. The two chief goals for most patients are to prolong survival and to improve health-related Quality of Life (QoL) [1]. Cancer-related fatigue, pain, anxiety and depression often co-occur as troublesome symptoms and are even referred to as the concept of 'symptom cluster'. They often arrive simultaneously and are responsible for reduced QoL and unfavorable prognosis [2]. Furthermore, fatigue, depression, cognitive impairment and insomnia are increasingly recognized as some of the most common side effects of conventional treatments for cancer. Research conducted in women with breast cancer suggests that the prevalence of moderate to severe fatigue during chemotherapy is 26% to 60%, depressive symptomatology 20% to 39% and self-reported insomnia even 79% [3,4]. A meta-analysis suggests that cancer patients exposed to adjuvant therapy perform worse on cognitive impairment than comparison groups (e.g., cancer patients who do not receive adjuvant therapy, non-cancer comparison group) or normative data [5]. These symptoms tend to be associated with reduced QoL [6], which was found to be prognostic and predictive of survival time in cancer patients [7].

Neuroendocrine-immune Model of Co-Morbidities and Cancer

The co-occurrence of fatigue, pain, anxiety, depression, insomnia and cognitive impairment indicates a common etiologic feature, which can be explained by a neuro endocrine-immune model [8]. This model states that these symptoms are mainly due to excessive inflammation. Multiple studies also state that other common features are Sympathetic Nervous System over activity (SNS) and increased oxidative stress [9,10]. However, the focus of this short communication will be on inflammation. And indeed, there is a massive production of circulating cytokines during cancer development that are enrolled in the systemic pain experienced by patients [8], in cancer-related fatigue, in anxiety and in depression and insomnia [11,12]. Importantly, the excessive inflammation is caused by the tumor on one hand and by conventional treatments on the other hand, such as chemotherapy and radiotherapy [13]. Though indeed successful, studies show that these treatments induce increases in inflammatory cytokines, which correlate with fatigue [11], with pain [14] and depression [12]. Treatments can also influence cognitive function through inflammatory processes. For example, cancer and chemotherapy-induced inflammation can increase levels of cytokines (e.g. IL-6), which can enter the brain and stimulate cells to produce other pro-inflammatory cytokines. Thus, deregulation can lead to DNA damage and cognitive damage [15]. Hence, the 'symptom cluster',

OPEN ACCESS

*Correspondence:

Marijke De Couck, Department of Mental Health, Wellbeing Research Group, Vrije Universiteit Brussel, Belgium,
E-mail: Marijke.de.couck@vub.be

Received Date: 14 Aug 2018

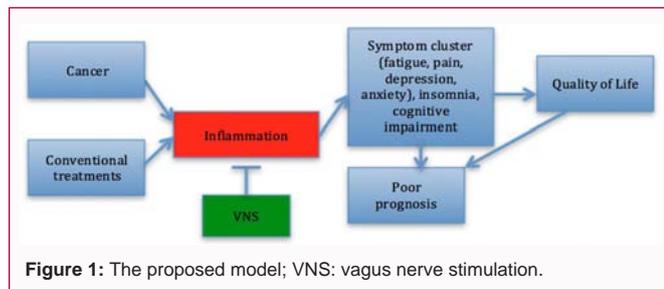
Accepted Date: 07 Sep 2018

Published Date: 13 Sep 2018

Citation:

De Couck M, Caers R. Why we Should Stimulate the Vagus Nerve in Cancer. *Clin Oncol.* 2018; 3: 1515.

Copyright © 2018 Marijke De Couck. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.



insomnia and cognitive impairment could be more severe during active treatment. On the other hand, these three mechanisms (SNS, oxidative stress and inflammation) and specifically inflammation contribute to *tumorigenesis* since the inflammatory response plays a key factor contributing to escape from apoptosis, angiogenesis and metastasis [16-18].

The Vagus Nerve as a Protective Factor

Finding new, scientifically based treatments, which target this etiological factor (and at the same time oxidative stress and sympathetic over activity), may improve these symptoms and prognosis. Recent research shows that the vagus nerve may have protective effects in various cancers. The vagus nerve is the main nerve of the parasympathetic system and has an important role in several diseases, including cancer [19]. This nerve inhibits oxidative stress, strongly inhibits inflammation [20] and as a parasympathetic nerve branch, it inhibits sympathetic activity, three mechanisms which are etiological to the symptoms and poor prognosis in cancer [21]. It has been shown that parasympathetic nervous system stimulation (via the vagus nerve) leads to decreases in production of pro-inflammatory cytokines through the release of the neurotransmitter acetylcholine [20,22]. The vagus nerve informs the brain about tumors and modulates them through feedback to neuro endocrine and immune systems [23]. Parasympathetic nervous activity is typically measured by capturing Heart Rate Variability (HRV), which is the variation of time between consecutive heartbeats in the ECG [24], thus low HRV reflecting a low vagus nerve activity.

Relation between HRV and Prognosis

The vagus nerve is thought to slow tumorigenesis through the inhibition of pro-inflammatory cytokines [10,24,25] showed that the index of vagus nerve activity, Heart Rate Variability (HRV), is significantly lower in cancer patients than in healthy people (HRV=20 vs. 50, p<0.001) and specifically in the metastatic stages. Additionally, our team has shown that high vagus nerve activity predicted less tumor burden and longer survival times in several types of cancer such as non-small cell lung, prostate, pancreatic and colon cancer, independent of confounders [10,26,27], echoed by other teams in breast cancer and other types [19,28]. The team of Spiegel showed that a higher vagus nerve activity in patients with metastatic or recurrent breast cancer strongly and significantly predicted a longer survival [29]. Furthermore, our team has shown that HRV predicts tumor burden very strongly, and especially in patients with metastatic cancer [10]. Recently, we also found that initially advanced tumor stages of colorectal or prostate cancer predicted higher tumor marker levels at follow-up than did early stages. However, this occurred only in patients with low, not high, vagal nerve activity (measured via HRV) [30]. In another study, we showed for the first time the prognostic value of a new composite biomarker, which reflects the

autonomic and immune (inflammatory) systems together, in relation to cancer prognosis. Two studies revealed that a new Neuroimmuno Modulation (NIM) index, reflecting vagal nerve activity (ratio of the Root Mean Square of Successive Differences (RMSSD)) over general systemic inflammation (CRP) significantly predicted the overall survival in patients with advanced pancreatic cancer and in patients with non-small cell lung cancer. These relationships remained significant also after statistically controlling for confounders which were univariately predictive of survival and which reflected the severity of cancer and its treatment. Patients with non-small cell lung cancer and a relatively high NIM index had a nearly double survival time compared to those with low NIM [31].

Relation between HRV and Symptoms

Furthermore, besides the negative effects of low Heart Rate Variability (HRV) on tumor burden, studies showed relations between low HRV and fatigue, pain, anxiety, depression, insomnia and cognitive impairment. An association between lower parasympathetic activity and higher levels of fatigue in breast cancer survivors has been shown [32], some studies showing inflammation to be the mediating factor. Two reviews and meta-analyses showed that HRV is significantly lower in people with severe depression than in subjects without depression [33]. Another meta-analysis showed that chronic pain patients have a reduced HRV compared to healthy people and that experimentally-induced pain in healthy people even reduces HRV [34]. A study in cancer patients showed that patients with depression and anxiety for a surgery had a significantly reduced HRV compared to patients without depression or anxiety [35]. Examining specific aspects of QOL related to cancer, vagus nerve activity is inversely related to pain (r= -0.46, p<0.05) and its activity may reduce pain [14]. HRV is also inversely related to sleep disturbances, to cognitive impairment and to hopelessness [36,37]. Finally, vagus activity also contributes to self-regulation of emotion and social activity [38] and is linked to treatment adherence in breast cancer. The study of Karvinen et al. suggested that breast cancer survivors who indicate the greatest stress reactivity tend to have the poorest compliance to medical care and the lowest QOL. The data suggest that supportive care strategies that reduce stress could potentially improve compliance to medical care in breast cancer survivors.

Vagus Nerve Stimulation

The vagus nerve can be stimulated pharmacologically, invasively and non-invasively. An implanted human Vagus Nerve Stimulation (VNS) device has been FDA approved for refractory epilepsy for more than 10 years and is undergoing clinical trials for resistant depression [40]. Direct electrical stimulation of the vagus nerve attenuates TNF α -production during experimental models of endotoxaemia, haemorrhagic shock, and other conditions of cytokine excess [41]. Furthermore, some non-invasive techniques to stimulate the vagus nerve exist as well. Transcutaneous Vagus Nerve Stimulation (t-VNS) (GammaCore and Cerbomed) has been shown to attenuate levels of the inflammatory mediator High Mobility Group Box 1 (HMGB1) and improve survival in a murine sepsis model [42]. In a recent study, a new t-VNS device was also found to reduce various inflammatory markers in humans [43] and to reduce depression by 50%, in two recent human trials [44]. Furthermore, tVNS was found to reduce headaches in patients with chronic migraines [45].

Studies have also demonstrated that multiple forms of meditation

can alter the parasympathetic component of HRV and can have a positive effect on cardiac autonomic tone [46]. Similarly, relaxation therapy and HRV biofeedback, both behavioural methods, can significantly increase the parasympathetic component of HRV, reflecting an increase in vagus nerve activity [47]. Furthermore, some therapeutic agents targeting the cholinergic anti-inflammatory pathway through action on the vagus nerve have been developed. Examples are the anti-inflammatory compound GTS-21 and CNI-1493, also called semapimod, which is a drug working via an intact vagus nerve. An increased efferent vagus nerve activity has been observed after administration of semapimod, demonstrating its vagal activating potential [48]. Only two studies investigated the effects of Semapimod and one pilot study the effects of HRV-Biofeedback directly on cancer. [49] investigated the effects of CNI-1493 and when comparing the tumour volumes in the control group versus the group who received CNI-1493, a smaller tumour volume was found in the latter (though they did not statistically test this) [50]. On the other hand showed that activation of vagus nerve with Semapimod decreases metastasis of murine breast carcinoma. A recent matched-controlled pilot study of our group (De Couck et al. submitted) showed positive effects of HRV-Biofeedback (HRV-B) in metastatic colon cancer patients. While in controls Carcinoembryonic Antigen (CEA) levels hardly changed, patients performing HRV-B showed a clear sharp decline in CEA levels, which by three months tended to be significantly lower than in controls ($p < 0.06$) (De Couck et al., submitted).

VNS to Reduce Chemotherapy-Induced and Radiotherapy-Induced Inflammation

Can VNS be combined with cancer treatments? Common treatments are chemotherapy and radiotherapy. Though successful, studies show that both therapies cause up regulation of stress response genes including NF κ B, that in turn up regulate the production of pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α [51], which correlate with the symptoms mentioned above. Such inflammation may also promote tumorigenesis [16]. Because vagus nerve stimulation reduces inflammation [20], VNS may also reduce therapy-induced inflammation and its undesirable side effects. Thus, VNS may potentially also augment the effectiveness of treatments (Figure 1). Furthermore, a recent research proposes that inflammation prior to radiation may make some types of lung cancer cells radio resistant [52]. Management of these symptoms, due to the cancer and the treatments and augment effectiveness of therapy is an important issue [7] and is the focus of the short communication at hand.

References

- Bottomley A, Flechtner H, Efficace F, Vanvoorden V, Coens C, Therasse P, et al. Health related quality of life outcomes in cancer clinical trials. *Eur J Cancer*. 2005;41(12):1697-709.
- Chida Y, Steptoe A. Positive psychological well-being and mortality: a quantitative review of prospective observational studies. *Psychosom Med*. 2008;70(7):741-56.
- Andrykowski MA, Schmidt JE, Salsman JM, Beacham AO, Jacobsen PB. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. *J Clin Oncol*. 2005;23(27):6613-22.
- Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. *J Clin Oncol*. 2010;28(2):292-8.
- Jim HS, Phillips KM, Chait S, Faul LA, Popa MA, Lee Y-H, et al. Meta-analysis of cognitive functioning in breast cancer survivors previously treated with standard-dose chemotherapy. *J Clin Oncol*. 2012;30(29):3578-87.
- Redeker NS, Lev EL, Ruggiero J. Insomnia, fatigue, anxiety, depression, and quality of life of cancer patients undergoing chemotherapy. *Sch Inq Nurs Pract*. 2000;14(4):275-90.
- Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res*. 2008;27:32.
- Miller AH, Ancoli-Israel S, Bower JE, Capuron L, Irwin MR. Neuroendocrine-immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol*. 2008;26(6):971-82.
- Panis C, Pavanelli WR. Cytokines as Mediators of Pain-Related Process in Breast Cancer. *Mediators Inflamm*. 2015;129034.
- De Couck M, Gidron Y. Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients. *Cancer Epidemiol*. 2013;37(5):737-41.
- Schubert C, Hong S, Natarajan L, Mills PJ, Dimsdale JE. The association between fatigue and inflammatory marker levels in cancer patients: a quantitative review. *Brain Behav Immun*. 2007;21(4):413-27.
- Haberkorn J, Burbaum C, Fritzsche K, Geser W, Fuchs D, Ocaña-Peinado FM, et al. Day-to-day cause-effect relations between cellular immune activity, fatigue and mood in a patient with prior breast cancer and current cancer-related fatigue and depression. *Psychoneuroendocrinology*. 2013;38(10):2366-72.
- Vyas D, Laput G, Vyas AK. Chemotherapy-enhanced inflammation may lead to the failure of therapy and metastasis. *Onco Targets Ther*. 2014;7:1015-23.
- De Couck M, Nijs J, Gidron Y. You may need a nerve to treat pain: the neurobiological rationale for vagal nerve activation in pain management. *Clin J Pain*. 2014;30(12):1099-105.
- Loh KP, Janelins MC, Mohile SG, Holmes HM, Hsu T, Inouye SK, et al. Chemotherapy-related cognitive impairment in older patients with cancer. *J Geriatr Oncol*. 2016;7(4):270-80.
- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436-44.
- Pikarsky E, Porat RM, Stein I, Abramovitch R, Amit S, Kasem S, et al. NF-kappaB functions as a tumour promoter in inflammation-associated cancer. *Nature*. 2004;431(7007):461-6.
- Voronov E, Shouval DS, Krelin Y, Cagnano E, Benharroch D, Iwakura Y, et al. IL-1 is required for tumor invasiveness and angiogenesis. *Proc Natl Acad Sci*. 2003;100(5):2645-50.
- De Couck M, Caers R, Spiegel D, Gidron Y. The role of the vagus nerve in cancer prognosis: A comprehensive review. *Journal of Oncology*. 2018;1236787.
- Tracey KJ. Reflex control of immunity. *Nat Rev Immunol*. 2009;9:418-28.
- De Couck M, van Brummelen D, Schallier D, De Grève J, Gidron Y. The relationship between vagal nerve activity and clinical outcomes in prostate and non-small cell lung cancer patients. *Oncol Rep*. 2013;30(5):2435-41.
- Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853-9.
- Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation*. 1996;93(5):1043-65.
- Gidron Y, Perry H, Glennie M. The vagus may inform the brain about sub-clinical tumors and modulate them: an Hypothesis. *Lancet Oncol*. 2005;6:245-8.

25. De Couck M, Mravec B, Gidron Y. You may need the vagus nerve to understand pathophysiology and to treat diseases. *Clin Sci*. 2012;122(7):323-8.
26. De Couck M, Maréchal R, Moorthamers S, Van Laethem JL, Gidron Y. Vagal nerve activity predicts overall survival in metastatic pancreatic cancer, mediated by inflammation. *Cancer Epidemiol*. 2016;40:47-51.
27. Mouton C, Ronson A, Razavi D, Delhaye F, Kupper N, Paesmans M, et al. The relationship between heart rate variability and time-course of carcinoembryonic antigen in colorectal cancer. *Auton Neurosci*. 2012;166(1-2):96-9.
28. Zhou X, Ma Z, Zhang L, Zhou S, Wang J, Wang B, et al. Heart rate variability in the prediction of survival in patients with cancer: A systematic review and meta-analysis. *J Psychosom Res*. 2016;89:20-5.
29. Giese-Davis J, Wilhelm FH, Tamagawa R, Palesh O, Neri E, Taylor CB, et al. Higher vagal activity as related to survival in patients with advanced breast cancer: an analysis of autonomic dysregulation. *Psychosom Med*. 2015;77(4):346-55.
30. Gidron Y, De Couck M, De Greve J. If you have an active vagus nerve, cancer stage may no longer be important. *J Biol Regul Homeost Agents*. 2014;28(2):195-201.
31. Gidron Y, De Couck M, Schallier D, De Greve J, Van Laethem JL, Maréchal R. The Relationship between a New Biomarker of Vagal Neuroimmune modulation and Survival in Two Fatal Cancers. *J Immunological Res*. 2018:4874193.
32. Crosswell AD, Lockwood KG, Ganz PA, Bower JE. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology*. 2014;45:58-66.
33. Huang M, Shah A, Su S, Goldberg J, Lampert RJ, Levantsevych OM, et al. Association of Depressive Symptoms and Heart Rate Variability in Vietnam War-Era Twins: A Longitudinal Twin Difference Study. *JAMA Psychiatry*. 2018;75(7):705-12.
34. Koenig J, Falvay D, Clamor A, Wagner J, Jarczok MN, Ellis RJ, et al. Pneumogastric (Vagus) Nerve Activity Indexed by Heart Rate Variability in Chronic Pain Patients Compared to Healthy Controls: A Systematic Review and Meta-Analysis. *Pain Physician*. 2016;19(1):E55-78.
35. Kim EH, Park JH, Lee SM, Gwak MS, Kim GS, Kim MH. Preoperative depressed mood and perioperative heart rate variability in patients with hepatic cancer. *J Clin Anesth*. 2016;35:332-338.
36. Hovland A, Pallesen S, Hammar A, Hansen AL, Thayer JF, Sivertsen B, et al. Subjective sleep quality in relation to inhibition and heart rate variability in patients with panic disorder. *J Affect Disord*. 2013;150(1):152-5.
37. Schwarz AM, Schächinger H, Adler RH, Goetz SM. Hopelessness is associated with decreased heart rate variability during championship chess games. *Psychosom Med*. 2003;65(4):658-61.
38. Thayer JF, Ahs F, Fredrikson M, Sollers JJ 3rd, Wager TD. A meta-analysis of heart rate variability and neuro imaging studies: implications for heart rate variability as a marker of stress and health. *Neuro sci Biobehav Rev*. 2012;36(2):747-56.
39. Karvinen K, Murray N, Arastu H, Allison R. Stress reactivity, health behaviors, and compliance to medical care in breast cancer survivors. *Oncol Nurs Forum*. 2013;40(2):149-56.
40. Corcoran C, Connor TJ, O'Keane V, Garland MR. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report. *Neuroimmunomodulation*. 2005;12(5):307-9.
41. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458-62.
42. Huston JM, Gallowitsch-Puerta M, Ochani M, Ochani K, Yuan R, Rosas-Ballina M, et al. Transcutaneous vagus nerve stimulation reduces serum high mobility group box 1 levels and improves survival in murine sepsis. *Crit Care Med*. 2007;35(12):2762-8.
43. Brock C, Brock B, Aziz Q, Møller HJ, Pfeiffer Jensen M, Drewes AM, et al. Transcutaneous cervical vagal nerve stimulation modulates cardiac vagal tone and tumor necrosis factor-alpha. *Neurogastroenterol Motil*. 2017;29(5).
44. Hein E, Nowak M, Kiess O, Biermann T, Bayerlein K, Kornhuber J, et al. Auricular transcutaneous electrical nerve stimulation in depressed patients: a randomized controlled pilot study. *J Neural Transm*. 2013;120(5):821-7.
45. Silberstein SD, Mechtler LL, Kudrow DB, Calhoun AH, McClure C, Saper JR, et al. Non-invasive vagus nerve stimulation for the acute treatment of cluster headache: findings from the randomized, double-blind, sham-controlled ACT1 study. *Headache*. 2016;56(8):1317-32.
46. Paul-Labrador M, Polk D, Dwyer JH, Velasquez I, Nidich S, Rainforth M, et al. Effects of a randomized controlled trial of transcendental meditation on components of the metabolic syndrome in subjects with coronary heart disease. *Arch Intern Med*. 2006;166(11):1218-24.
47. Sakakibara M, Hayano J, Oikawa LO, Katsamanis M, Lehrer P. Heart rate variability biofeedback improves cardio respiratory resting function during sleep. *Appl Psychophysiol Biofeedback*. 2013;38(4):265-71.
48. Pavlov VA, Ochani M, Gallowitsch-Puerta M, Ochani K, Huston JM, Czura CJ, et al. Central muscarinic cholinergic regulation of the systemic inflammatory response during endotoxemia. *Proc Natl Acad Sci U S A*. 2006;103(13):5219-23.
49. Kemeny MM, Botchkina GI, Ochani M, Bianchi M, Urmacher C, Tracey KJ. The tetravalent guanlylhydrazone CNI-1493 blocks the toxic effects of interleukin-2 without diminishing antitumor efficacy. *Proc Natl Acad Sci U S A*. 1998;95(8):4561-6.
50. Erin N, Duymuş O, Oztürk S, Demir N. Activation of vagus nerve by semapimod alters substance P levels and decreases breast cancer metastasis. *Regul Pept*. 2012;179(1-3):101-8.
51. Kim W, Youn H, Kang C, Youn B. Inflammation-induced radio resistance is mediated by ROS-dependent
52. inactivation of protein phosphatase 1 in non-small cell lung cancer cells. *Apoptosis*. 2015;20(9):1242-52.
53. Sultani M, Stringer AM, Bowen JM, Gibson RJ. Anti-Inflammatory Cytokines: Important Immunoregulatory Factors Contributing to Chemotherapy-Induced Gastrointestinal Mucositis. *Chemother Res Pract*. 2012;490804.