Cancer Epidemiology 40 (2016) 47–51

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Vagal nerve activity predicts overall survival in metastatic pancreatic cancer, mediated by inflammation

Marijke De Couck[a,*], Raphaël Maréchal[b], Sofie Moorthamers[c], Jean-Luc Van Laethem[b], Yori Gidron[c]

[a] Mental Health and Wellbeing Research Group, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), 103 Laarbeeklaan, 1090 Brussels, Belgium
[b] Department of Gastroenterology, GI Cancer Unit Erasme Universitary Hospital Université Libre de Bruxelles, 808, route de Lennik, 1070 Brussels, Belgium
[c] Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel (VUB), 103 Laarbeeklaan, 1090 Brussels, Belgium

ARTICLE INFO

Article history:
Received 22 September 2015
Received in revised form 10 November 2015
Accepted 13 November 2015
Available online xxx

Keywords:
Autonomic nervous system
Vagus nerve
Pancreatic cancer
Neuroimmuno-modulation
Inflammation

ABSTRACT

Recent research findings suggest neuro-modulation of tumors. Finding new modifiable prognostic factors paves the way for additional treatments, which is crucial in advanced cancer, particularly pancreatic cancer. This study examined the relationship between vagal nerve activity, indexed by heart rate variability (HRV), and overall survival (OS) in patients ($N = 272$) with advanced pancreatic cancer. A "historical prospective" design was employed, where vagal activity and other confounders were retroactively obtained from medical charts at diagnosis, and subsequent OS was examined. HRV was obtained from 10 sec ECGs near diagnosis. Levels of C-reactive protein (CRP) were measured as an inflammatory marker. OS and survival date were obtained from medical charts and the Belgian national registry. Patients with high HRV (>20 msec) survived on average more than double the days (133.5) than those with low HRV (64.0). In a multivariate cox regression, higher initial HRV was significantly correlated with lower risk of death, independent of confounders including age and cancer treatments. This relationship was statistically mediated (accounted for) by CRP levels. Importantly, in patients who lived up to one month from diagnosis only, HRV was unrelated to CRP, while in patients surviving longer, HRV was significantly inversely related to CRP ($r = -0.20$, $p < 0.05$). These results are in line with possible vagal nerve protection in a fatal cancer, and propose that the mechanism may involve neuroimmuno-modulation. Future studies must test whether vagal nerve activation may help patients with advanced cancers.

1. Introduction

Tumors progress under the influence of oxidative stress, inflammation and excessive sympathetic activity. For example, Voronov et al. [1] showed that in IL-1 beta knockout mice, lung metastases of B16 melanoma cells were not observed compared with wild-type mice. Furthermore, inherent oxidative stress also affects several functions in cancer cells or tumour tissues, such as cell proliferation, promotion of mutations and genetic instability, alterations in cellular sensitivity to anticancer agents, invasion, angiogenesis and metastasis [2]. A third mechanism linked to cancer progression is excessive sympathetic activity, which was found to promote tumors [3,4].

On the other hand, the vagus nerve, which is a major component of the parasympathetic nervous system, may slow tumor progression [5]. The vagus nerve can inhibit oxidative stress, inflammation and excessive sympathetic activity [6–8]. The vagus nerve represents an important channel for the bidirectional communication between the brain and the immune system [7]. Via the production of inflammatory cytokines, the immune system can activate sensory fibers of the vagus nerve expressing receptors for interleukin-1, that ascend to synapses in the nucleus tractus solitaries (NTS) in the brain stem. In return, the activated effector neurons of the vagus nerve can inhibit the production of peripheral pro-inflammatory cytokines via binding of acetylcholine on tissue macrophages. This negative feedback-loop system is the core of the nicotinic anti-inflammatory pathway [7], any may render the vagus tumor-protective roles. Indeed, tumor-bearing animals undergoing chemical or surgical vagotomy showed enhanced metastasis [9,10], while an anti-inflammatory drug (CNI-1493),

* Corresponding author.
E-mail address: marijke.de.couck@vub.ac.be (M.D. Couck).

http://dx.doi.org/10.1016/j.canep.2015.11.007
1877-7821/

whose action depends on and stimulates the vagus nerve [11], reduced tumor size and metastases in tumor-bearing mice [12].

In cancer patients, high vagal nerve activity, indexed by heart rate variability (HRV) [13], significantly predicted lower tumor marker levels and longer overall survival (e.g. [14–16]). As mentioned above, inflammation promotes tumorigenesis [1,17], but it is strongly inhibited by vagal nerve activity [7]. However, the role of vagal neuroimmuno-modulation in cancer prognosis was not tested. This study tested whether HRV at diagnosis was independently correlated with overall survival in patients with advanced pancreatic cancer. Furthermore, we preliminarily investigated the role of inflammation in this relationship. We hypothesize that high baseline HRV would be associated with longer survival and that this relationship would be statistically mediated (accounted) by lower levels of inflammation. Finally, we examined whether the HRV-CRP relationship (reflecting neuro-immuno-modulation), is associated with survival time as well.

2. Patients and methods

2.1. Design

The present study used an "historical-prospective design". We obtained existing archival data on patients' medical background and HRV, and then examined the prospective relationship between these parameters measured at diagnosis and patients' overall survival (OS). The design term "historical-prospective" is commonly used in reanalysis of existing longitudinal datasets.

2.2. Patient cohort

After approval of the Medical Ethics Committee, medical records of 620 patients with histologically proven advanced (locally advanced and metastatic) pancreatic cancer (PC) treated at the University Hospital Erasme, Brussels, between 1998 and 2011, were reviewed. Tumor staging was made based on chest and abdominal CT-scan, magnetic-resonance imagery, and endoscopic ultrasound findings. Exclusion criteria included chronic inflammatory disease, anemia and thyroid disease or lack of an ECG taken near the time of diagnosis. Following these exclusion criteria, $N = 353$ patients were included, of whom survival data were certified for $N = 272$ patients. There were no statistically significant differences in various background variables, treatments or HRV levels between patients with and without survival data ($p > 0.05$ for all). However, there were significantly fewer patients undergoing surgery (44.6% versus 62.5%, $p < 0.05$) in the sample with survival data than in those without survival data. Our study sample included 52.8% patients with locally advanced cancer and 47.2% with metastatic cancer and their mean age was 60.0 ($\pm$11.5) years. The sample size of this study was anticipated to be sufficiently large, as it exceeded De Couck et al. [16] showing a significant correlation between HRV and survival time in $N = 73$ lung cancer patients.

2.3. Variables

2.3.1. Background confounders

These included age, gender, treatments (radiotherapy, chemotherapy, surgery), locally advanced versus metastatic PC, and presence of cardiac disease. These data were obtained from patients' electronic medical records.

2.3.2. Vagal nerve activity

Heart rate variability (HRV), the index of vagal nerve activity, was derived from patients' 10 sec ECG near diagnosis. This represents efferent vagal nerve input to the heart. HRV has been shown to be strongly correlated with and to be experimentally altered by vagal nerve activity [13,18]. The time domain parameters 'standard deviation of normal R–R intervals' (SDNN), in msec, and the root mean square of successive differences (RMSSD) between preceding R–R intervals, were derived. Such parameters from short ECGs have been found to correlate with ECGs of longer durations [19]. Furthermore, 10 sec SDNN measures have been shown to predict prognosis in cardiac disease [20], and in colon cancer [15]. A cut-off of 20 msec was used, as in past studies in cancer [15,20], to distinguish between patients with high versus low HRV. Furthermore, 20 msec has been shown to be the mean HRV in a big sample of cancer patients ($N = 657$) [21].

2.3.3. Inflammatory marker

We obtained from patients' medical records levels of C-Reactive Protein (CRP) near diagnosis, a systemic inflammatory marker of prognostic value in many cancers, including PC [22].

2.4. Outcomes

The primary outcome in the present study was overall survival (OS), obtained from medical charts and the Belgian national registry. We used as censorship date November 1st, 2012, the last date of inspecting patients' medical files.

2.5. Statistical analysis

We first performed a multivariate Cox-regression analysis using all confounders, except for HRV, for predicting OS. This enabled all confounders to 'compete' in independently predicting OS. In this analysis, death (OS) was the dependent variable, and time till death or censorship date (for alive patients) was the time variable. The relationship between HRV and OS was tested with a univariate Cox-regression, followed by a multivariate Cox-regression with all other significant confounders. A two-tailed statistical significance of $p < 0.05$ was used. To determine statistically the mediating (explanatory) role of CRP, we performed two tests. First, we examined the relationship between CRP and HRV and OS. Then, we reexamined the relationship between HRV and OS, while statistically controlling for all confounders as well as for CRP in the Cox-regression. Second, we conducted a Sobel test on survival time (in days) and examined the Pearson's correlation between HRV and CRP and between each with survival time. We then examined whether the HRV—survival time correlation remained significant, after statistically controlling for CRP. Then, we examined whether the CRP-Survival time relationship remained after statistically controlling for HRV.

Finally, to gain insight into the neuroimmuno-modulatory role of the vagus nerve in cancer, we examined the expected negative relationship between HRV and CRP in patients surviving up to one month versus in patients surviving over one month. Though the median survival time was 41 days, approximately one third of the sample survived up to one month, which was chosen as a clinically relevant and more tangible cut-off. A similar pattern was found when taking the median survival time.

3. Results

3.1. Sample characteristics

Table 1 depicts the characteristics of the present sample, on which survival data were available ($N = 272$ patients). Patients' mean age was 60 years, their mean HRV at diagnosis was very low (SDNN = 21.7 msec), yet similar to those in other cancers [16]. The mean CRP levels near diagnosis were elevated compared to some proposed cut-offs (e.g., 3 mg/L) [23]. Approximately half of the