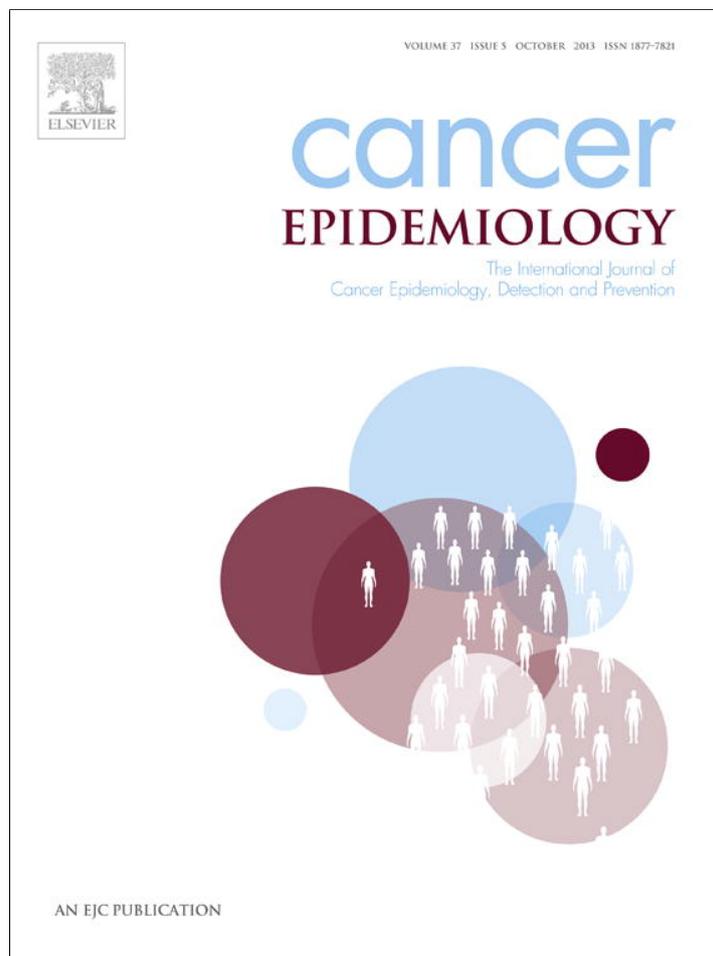


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Norms of vagal nerve activity, indexed by Heart Rate Variability, in cancer patients

M. De Couck*, Y. Gidron

Faculty of Medicine and Pharmacy, Free University of Brussels (VUB), Belgium

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ABSTRACT

Recent research has begun to show the role of the activity of the vagus nerve in cancer prognosis. However, it remains unknown whether cancer severity can impair vagal nerve activity. This study combined data ($N = 657$) of five different cancers (colorectal, pancreas, prostate, lung and ovarian) concerning patients' Heart Rate Variability (HRV), a vagal nerve activity index. These data were compared to HRV levels of a healthy sample in another study. In addition, we examined the moderating effects of age, gender and cancer stage on HRV. The mean HRV of the cancer patients sample was significantly lower (HRV = 22 ms) compared to the healthy sample (HRV = 50 ms) ($p < 0.000001$). While age and gender did not significantly affect HRV, cancer patients with advanced stages had significantly lower HRV than those with early stages ($p = 0.011$). A possible bi-directional relation between cancer and vagal nerve activity is discussed. These findings are of importance for prognostication since they provide researchers and clinicians with expected values of vagal nerve activity in cancer patients.

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1. Introduction

The vagus nerve is one of the ten cranial nerves, and constitutes the main nerve of the parasympathetic nervous system. An important non-invasive index of vagal nerve activity is Heart Rate Variability (HRV), which is the variation in the beat-to-beat interval (RR interval in the electrocardiogram). HRV is highly correlated with vagal nerve activity ($r = 0.88$) [1] and mainly reflects efferent cardiac vagal nerve activity. HRV was found in numerous studies to predict onset and prognosis in multiple diseases including risk of new cardiac events in healthy people [2], sudden death after a myocardial infarction [3], death in renal failure patients [4], as well as short-term critical outcomes in pre-hospital ambulance patients [5]. Thus, there has been increasing interest in the measurement of HRV and establishing norms associated with risk.

Recent studies have also begun to examine the prognostic role of vagal nerve activity indexed by HRV in cancer. It has been hypothesized that vagus nerve activity may modulate tumor growth, since it inhibits tumor-promoting mechanisms [6,7]. Three important basic mechanisms have been shown to play a pivotal role in tumourigenesis.

The first mechanism is oxidative stress [8] which leads to both DNA-damage, a central trigger of tumourigenesis, and to uncontrolled cell proliferation [9]. Furthermore, DNA damage and oxidative stress are also predictive factors of cancer prognosis [10]. The second mechanism is local excessive inflammation that promotes tumourigenesis in early stages of oncogenesis [11], and disease progression in its later stages [12,13]. The inflammatory microenvironment which is normally recruited to help fighting and eliminating the tumors, is thus also promoting tumor growth and producing free radicals to further induce oxidative stress. Finally, the metastatic process is under the control of sympathetic neurotransmitters e.g. norepinephrine, which enhance the migratory capacity of cancer cells, and determine the direction and the development of metastases [14]. Vagal nerve activity on the other hand, is inversely related to and inhibits these three mechanisms [7,15–18]. Based on converging evidence, Gidron et al. [6] and Mravec et al. [19] hypothesized that adequate vagal nerve activity may modulate tumor growth. If valid, vagal nerve activity (HRV) might become a variable that could be used as a prognostic factor and could be therapeutically manipulated to improve prognosis. High HRV has been shown to predict longer cancer survival and reduced tumor burden [20–22]. However, those studies had small sample sizes and did not control for any confounder. A following study [23] showed that HRV was a significant predictor of survival time in terminal cancer patients, independent of confounders. We recently showed that low HRV predicts increases in the colon cancer marker Carcinoembryonic Antigen (CEA) and in the prostate cancer marker (PSA), independent of confounders and excluding cardiac patients [24,25]. Furthermore, a positive correlation was

* Corresponding author at: Faculty of Medicine and Pharmacy, Free University of Brussels (VUB), 103, Laarbeeklaan, 1090 Jette (Brussels), Belgium.
 Tel.: +32 2 477 41 02; fax: +32 2 477 41 59.

E-mail address: marijke.de.couck@vub.ac.be (M. De Couck).

shown between HRV and survival time in younger non-small cell lung cancer patients (age <65 years old) [25]. However, the design of these studies is correlational, albeit prospective or “historical prospective”. Supporting a causal relation, some experimental studies have shown that lacking an intact vagus (vagusotomy) leads to worse prognosis in cancer [26,27]. Furthermore, a causal relation between vagal nerve activation, by administering an anti-inflammatory drug acting via the vagus nerve, known as CNI-1493, and reduced tumor volume has recently been shown [28]. All these studies emphasize the importance of vagal nerve activity in cancer prognosis. Given the consistency of past studies, vagal nerve activity may emerge as a new biomarker with independent prognostic value in cancer. Consequently, it seems important to investigate the norms of HRV values across cancer patients, which was the aim of this study.

However, the link between vagal nerve activity and cancer may be bidirectional. One could argue that vagal nerve activity may also be affected by cancer and thus be impaired in cancer patients. In the study by Mouton et al. [24], patients who had lower HRV at baseline had higher tumor marker levels at baseline and at follow-up. It is possible that their worse initial tumor burden led to lower vagal activity. This study examined HRV parameters in five different groups of cancer patients and explored the roles of age, gender and stage. Furthermore, the HRV parameters were compared with those of a healthy sample in a prior study. Together, these enabled us to establish expected values concerning HRV in cancer patients and to preliminarily investigate the influence disease severity on HRV.

2. Methods

2.1. Design

This study used a retrospective design since medical archival data were analyzed.

2.2. Participants

After approval of the Medical Ethics Committee, medical records of 246 colorectal cancer (CRC) patients and 220 ovarian cancer patients (OC) treated at the Jules Bordet Hospital, Brussels, between March 2001 and December 2006, were reviewed. The same procedure was done in the University Hospital of Brussels where the medical records of 620 patients with prostate cancer (PrC) and 650 patients with non-small cell lung cancer (NSCLC) treated between January 2005 and December 2009, were reviewed. Finally, after approval of the Medical Ethics Committee, medical records of 620 metastatic and 150 resectable pancreatic cancer patients (PaC) treated at the University Hospital Erasme, Brussels, were reviewed. Exclusion criteria included conditions known to alter HRV or influence inflammation such as heart diseases, treatments with anti-arrhythmic drugs or beta-blockers, pacemaker, chronic inflammatory disease, anemia and thyroid disease. Following these exclusion criteria, we finally examined the data of $N = 72$ colorectal cancer (CRC) patients, $N = 58$ ovarian cancer (OC) patients, $N = 113$ prostate cancer (PrC) patients, $N = 133$ non-small cell lung cancer (NSCLC) patients, $N = 49$ resectable and $N = 236$ metastatic pancreatic cancer (PaC) patients.

2.3. Measures

2.3.1. Background data

For each cancer, background information included gender, age and cancer stage at diagnosis.

2.3.2. Vagus nerve activity

Vagal nerve activity was indexed by deriving Heart Rate Variability (HRV) from patients' 10-s ECG obtained near diagnosis. HRV is highly correlated with vagal nerve activity ($r = 0.88$) [1] and mainly reflects efferent cardiac vagal nerve activity. For certain HRV parameters, such short ECGs have been found to correlate with ECGs of longer durations (5 and 10 min) [29,30]. Parasympathetic nerve traffic enacts its effects at a much faster (<1 s) rate than sympathetic outflow (>5 s). Therefore, beat-to-beat changes in RR intervals are considered to be mainly a reflection of vagal outflow [31]. The time domain parameter ‘standard deviation of normal beat to beat intervals’, named SDNN (in ms), and ‘root mean square successive difference’, named RMSSD (in ms) were derived. 10 s SDNN has been shown to predict tumor marker levels in colon cancer [24] and prognosis in cardiac disease [32] as well as numerous outcomes mentioned above. The frequency domain parameters were not derived, since they require a longer ECG measurement [31].

2.4. Statistical analysis

This study was primarily a descriptive one, hence, we mainly provide means and standard deviations (SD) of HRV parameters for each cancer group, and then for age, stage and gender subgroups as well. Levels of HRV in the cancer groups were compared using an analysis of variance (ANOVA). For comparing the healthy sample with the cancer patients, we used a *t*-test.

3. Results

Descriptive statistics of the study variables are shown in Tables 1 and 2.

As shown in Table 1, most patients were diagnosed with metastatic cancer. The mean age of cancer diagnosis in the total sample is 63 years old, while ovarian cancer seems to occur in younger women. The SDNN and RMSSD in the total sample are respectively $21.65 \text{ ms} \pm 16.78$ and $23.79 \text{ ms} \pm 20.48$, as shown in Table 2.

We then examined the percentage of cancer patients with low and high HRV, using the cut-off of SDNN < 20 ms for low HRV from previous studies [24,32] and concluded that 59.5% of the total cancer patient sample had low HRV.

In Table 3, we split the samples by gender, age and stage. We used 65 years old as the cut-off since from that age comorbidities, such as cardiac disease, are known to occur, which influences HRV data [33,34]. Concerning stage, we split the patients into early (1–2) and late (3–4) stages. Furthermore, we log transformed the HRV parameters in the total sample, on which we performed the moderation analyses. A significant difference in log SDNN could be found between early and late stages ($p = 0.011$), with a lower SDNN in the late stages. A similar pattern was found when grouping patients into high and low SDNN. Among patients with severe stages, 62.3% had low HRV (<20 ms), while 52.7% of patients with early stages had low HRV ($\chi^2(1) = 4.96$; $p < 0.05$). Concerning age,

Table 1
Percentages of stage in the various cancer types.

Cancer type	Stage (I: %, II: %, III: %, IV: %)			
Prostate	I: 0	II: 66	III: 9	IV: 25
Pancreatic	I: 1	II: 16	III: 0	IV: 83
Colon	I: 26	II: 13	III: 28	IV: 33
Ovarian	I: 14	II: 7	III: 60	IV: 19
NSCLC	I: 16	II: 10	III: 20	IV: 54
All cancers	I: 8	II: 20	III: 14	IV: 58

NSCLC, non-small cell lung cancer.

Table 2
Descriptive statistics in the various cancer types.

Cancer type	Patients (N)	Gender (% men)	Age (year)	SDNN (ms)	RMSSD (ms)
Prostate	101	100	64.83 ± 8.91	27.27 ± 22.21	26.58 ± 25.67
Pancreatic	286	44	63.65 ± 11.95	22.63 ± 14.67	26.81 ± 19.14
Colon	72	39	63.71 ± 10.49	22.86 ± 18.94	23.85 ± 19.23
Ovarian	58	0	58.31 ± 11.71	18.95 ± 13.31	18.17 ± 11.6
NSCLC	133	65	62.22 ± 10.22	17.12 ± 14.6	19.07 ± 21.06
All cancers	657	53	63.09 ± 11.07	21.65 ± 16.78	23.79 ± 20.48

Data are presented as mean ± SD (standard deviation).

NSCLC, non-small cell lung cancer; Yr, year; ms, milliseconds; SDNN, standard deviation of normal beat to beat intervals; RMSSD, root mean square successive difference.

Table 3
Descriptive statistics in each cancer, split for gender, age and stage.

Cancer type	Men	Women	<65	>65	Stages 1–2	Stages 3–4
Prostate						
SDNN	27.27 ± 22.21		26 ± 17.9	28.5 ± 25.75	30.35 ± 23.28	25.01 ± 22.03
RMSSD	26.58 ± 25.67		23.26 ± 17.3	29.72 ± 31.46	30.24 ± 27.98	22.89 ± 25.2
Pancreatic						
SDNN	23.65 ± 14.95	21.83 ± 14.45	22.67 ± 13.01	22.59 ± 16.14	23.83 ± 14.88	22.38 ± 14.64
RMSSD	28.36 ± 20.56	25.6 ± 17.92	24.68 ± 14.56	28.84 ± 22.52	26.4 ± 18.39	26.89 ± 19.33
Colon						
SDNN	19.6 ± 16.41	24.92 ± 20.3	23.69 ± 20.1	22.03 ± 17.95	23.7 ± 18	22.33 ± 19.71
RMSSD	19.06 ± 13.53	26.9 ± 21.71	23.71 ± 19.35	24 ± 19.38	22.77 ± 14.9	24.53 ± 21.68
Ovarian						
SDNN		18.95 ± 13.31	23.34 ± 14.11	9.93 ± 3.54	22 ± 13.02	18.16 ± 13.41
RMSSD		18.17 ± 11.6	21.54 ± 12.63	11.26 ± 3.81	21.05 ± 12.07	17.42 ± 11.49
NSCLC						
SDNN	16.88 ± 13.88	17.57 ± 16.04	18.12 ± 14.99	15.89 ± 14.14	19.05 ± 23.09	16.64 ± 12.27
RMSSD	18.63 ± 20.7	19.9 ± 21.94	19.08 ± 19.4			15.64 ± 11.45
All cancers						
SDNN	22.14 ± 17.81	21.09 ± 15.54	22.09 ± 15.43	21.18 ± 18.13		23.79 ± 18.49
RMSSD	24.02 ± 22.16	23.54 ± 18.42	22.52 ± 16.61	25.16 ± 23.9		24.06 ± 20.71
All cancers						
Log SDNN	1.25 ± 0.31	1.23 ± 0.28	1.26 ± 0.28	1.22 ± 0.31		1.29 ± 0.29
Log RMSSD	1.27 ± 0.31	1.28 ± 0.26	1.27 ± 0.27	1.28 ± 0.31		1.27 ± 0.29

Data are presented as mean ± SD (standard deviation).

SDNN, standard deviation of normal beat to beat intervals; RMSSD, root mean square successive difference.

log SDNN tended to significantly decline with age ($p = 0.055$), with SDNN being higher in the group below age 65 years. Furthermore, SDNN of the ovarian cancer patients above 65 years old is significantly lower than the SDNN of the patients >65 years in the other cancer types, except for NSCLC ($p < 0.05$ in all). No difference could be found between men and women in HRV ($p > 0.05$). In general, the SDNN of ovarian cancer and NSCLC were significantly lower than those of the other 3 cancer types ($p < 0.05$). Since we had no a priori hypothesis concerning the differences in HRV between the different cancers, we do not report further comparisons.

We then compared the HRV parameters of the cancer patients with those of healthy adults, using the large sample of 21,438 healthy participants, whose HRV was measured using short-term protocol [35].

Both log SDNN and log RMSSD were significantly lower in the cancer sample than in the healthy people (respectively $t(22,093) = 280.77$; $p < 0.000001$; $t(22,093) = 213.83$; $p < 0.000001$) (see Table 4).

Table 4
Comparing HRV parameters of cancer patients and healthy people.

	SDNN (in ms)	RMSSD (in ms)	Log SDNN	Log RMSSD
Cancer patients	22 ± 17	24 ± 20	1.24 ± 0.29	1.28 ± 0.29
Healthy people	50 ± 16	42 ± 15	3.82 ± 0.23	3.49 ± 0.26

Data are presented as mean ± SD (standard deviation).

SDNN, standard deviation of normal beat to beat intervals; RMSSD, root mean square successive difference; ms, milliseconds.

4. Discussion

This study investigated the effect of cancer severity on vagal nerve activity, indexed by HRV.

We included 657 cancer patients with one of the five following cancer types: prostate (PrC), pancreatic (PaC), colorectal (CC), ovarian (OC) and non-small cell lung cancer (NSCLC). Patients with cardiac disease, or patients taking medication known to alter vagal nerve activity, were excluded. The SDNN and RMSSD in the total sample were respectively $22 \text{ ms} \pm 17$ and $24 \text{ ms} \pm 20$, which are considerably low. These means are in line with some previous studies [23], but not with others [20,21], which could be partly explained by the differences in length of HRV measurement. We observed a certain range of HRV between the cancer types. Multiple factors can hypothetically account for this, including the etiological factors (e.g. smoking, diet), genetics, age and different distributions of stage and metastatic site between the cancers (e.g. lung versus the other cancers).

We then explored possible moderators, by splitting the sample into early (1–2) and late (3–4) stages, and into both genders and young and old patients. In the total sample, patients in the early stages had a significantly higher HRV than patients in the later stages and this was seen also when using the cut-off of $\text{SDNN} < 20 \text{ ms}$. Though these cancers are not comparable, this could mean that disease severity influences HRV. During the metastatic stage, all three mechanisms thought to underlie the effects of vagus nerve activity on tumor burden, namely, excessive inflammation, oxidative stress and sympathetic activation [10,13,14] may bear a greater role on HRV. Another explanation

could be that cancer patients receive treatments (e.g. chemotherapy) which reduce vagal nerve activity [36]. However this did not occur in our data, since HRV was derived at time of diagnosis, before the start of treatment. Finally, the onset of other comorbidities as a result of the tumor/cancer, such as cardiac disease and reduced lung functioning, could cause a reduction, especially in the metastatic stages [33,34,37]. In general, the SDNN of ovarian cancer and NSCLC were significantly lower than those of the other 3 cancer types. This could be explained by the fact that ovarian carcinoma is a gynecologic malignancy with the highest case-to-fatality ratio [38]. Furthermore, the high mortality of this tumor is largely explained by the fact that the majority (75%) of patients present at an advanced stage, with widely metastatic disease within the peritoneal cavity. The low SDNN in lung cancer patients could be happening possibly due to the cancer-induced respiratory problems and the severity of the cancer burden in NSCLC. These two factors, and mainly the former, have an important impact on HRV.

Concerning age, HRV tended to significance, being higher in the group below 65 years old. This may be the result of the cumulative effects of cancer with comorbidities and age on multiple homeostatic systems, including the parasympathetic system [39]. In the ovarian patients above 65 years old, the SDNN is significantly lower than in the other cancer patients, except for NSCLC, of the same age group. This could be explained by the fact that the number in this group was rather small ($N = 19$) possibly rendering the more extremely low HRV cases more influence on the mean, and that all patients were diagnosed with an advanced stage, additionally reducing HRV. In the NSCLC patients above 65 years, the low SDNN could be explained by the respiratory problems and also by the fact that most patients were diagnosed with advanced cancer. At last, no difference could be found between men and women. This topic is controversial with some studies showing gender differences and others not [40–43], in healthy people.

The main question of the present study was whether vagal nerve activity in cancer patients is impaired compared to healthy people. Therefore, we used the review of Nunan et al. [35], which included 21,438 healthy participants. When comparing the two samples, both SDNN and RMSSD were significantly lower in the cancer sample than in healthy people. This significant difference could be explained via both directions of causality. First of all, tumors progress by three biological mechanisms, namely the presence of free radicals, excessive inflammation and sympathetic activity. These are known to reduce the activity of the vagus nerve. Experimental studies which induced inflammation resulted in reduced HRV [44]. Furthermore, oxidative stress is known to reduce HRV [17]. And perhaps the strongest factor is sympathetic nervous activity. The fear of having a tumor, the fear of consulting a doctor who might confirm the onset of a tumor, the period of uncertainty between the consultation and the final diagnosis, receiving the bad news about the prognosis, all the additional information, questions, uncertainties, unknowns about treatments, prognosis and development, these are all factors putting people under serious stress. Indeed, studies have found that stress reduces HRV [45]. However, we still notice ranges of HRV in patients with the same stage or gender, which could mean that people react differently to the same stressors. Personality, helplessness–hopelessness, way of living (diet, smoking), and social support may have a crucial role [46,47].

However, it is also possible that reduced vagal nerve activity is a risk factor for cancer development and for developing a more advanced tumor stage. To the best of our knowledge, only one study tested this partly, prospectively. Dekker et al. [32] found that low HRV predicted increased risk of dying from cancer in a population study sample. Low HRV may not inhibit inflammatory

and oxidative responses to an evolving mutation, which could thus facilitate oncogenesis [11,48]. Insufficient vagal modulation of sympathetic activity could also favor tumor development and invasiveness [14]. Thus, the debate concerning the bidirectional relation between HRV and cancer severity remains open and needs further experimental and prospective testing.

This study has a few limitations. First, the HRV parameters are based on a 10-s ECG, taken at time of diagnosis. Although HRV data derived from 10-s ECG have been correlated with ECGs of 5 and 20 min and have been shown to predict cancer prognosis and cardiac disease, the Task Force recommends the shortest ECG to be 5 min [31]. Furthermore, ECG taken at time of diagnosis will include an increase in sympathetic activity since patients are in fear, uncertainty and under emotional stress. Since this was not a formal prospective design, we were not able to control the measure of HRV or include more background variables such as diet, stress levels, physical activity and family history. To address these limitations, future studies should conduct prospective studies, with more background variables and an ECG of minimum 5 min, taken at baseline and at a later time (for example after 3 months). This way, researchers could find out whether an improved prognosis due to treatment could also increase vagal nerve activity. On the other hand, this could also examine whether a worse cancer prognosis results from a reduction in HRV.

However, this study shows for the first time that cancer patients have a significantly lower HRV than healthy people and suggests that cancer severity may also affect vagal nerve activity. These findings are of importance for prognostication since they provide researchers and clinicians with expected values of vagal nerve activity in cancer patients. Indeed, low levels of HRV at diagnosis i.e. SDNN below 20 ms, have been shown to predict poor prognosis and were observed in high prevalence in our sample [24,25].

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