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EXPLORING THE ROLE OF VAGAL NERVE ACTIVITY IN THE COMPLEX RELATIONSHIP BETWEEN PSYCHOLOGICAL FACTORS AND CANCER

RÔLE DE L'ACTIVITÉ DU NERF VAGUE DANS LA RELATION COMPLEXE ENTRE LES FACTEURS PSYCHOLOGIQUES ET LE CANCER

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Point n'est besoin d'espérer pour entreprendre, ni de réussir pour persévérer

There is no need to hope to undertake, nor to succeed to persevere

Guillaume d'Orange

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ABSTRACT

The general aim of this thesis was to understand the role of the vagal nerve in cancer onset and to characterize its relationship with cancer risk factors. In the first chapter of this thesis, we presented how psychological factors, related to both mental health and health behaviors, could lead to DNA mutation, inflammation or excessive sympathetic activity, which will then influence cancer development. Indeed, we explained how chronic stress (resulting from depression, anxiety, or life events) might activate the sympathetic nervous system, and the hypothalamic pituitary adrenal (HPA) axis and affect the immune system and inflammation. We also highlighted how health behaviors influence biological mechanisms (e.g., inflammation and sympathetic activity). Those biological mechanisms are involved in every stage of cancer development, from mutagenesis to metastasis. In other words, psychological factors and biological mechanisms influencing cancer onset and prognosis have some common pathways.

The present thesis focused on a protective neural factor in cancer onset and more specifically on the roles of the vagal nerve as another possible relevant predictor of cancer onset. As presented in the second chapter, the vagal nerve is associated with psychological risk and prognostic factors, as well as with cancer prognosis. Indeed, lower values of heart-rate variability (HRV), the vagal index, are associated with risk and prognostic factors such as depression, anxiety, alcohol use and low physical activity. Moreover, the vagal nerve is a key component of the neuro-immune axis, which is involved in the regulation of the sympathetic and the inflammatory response (both involved in cancer development). Finally, HRV has a prognostic role in cancer survival. In conclusion, the vagal nerve is related to cancer risk factors, to the regulation of processes involved in cancer development and vagal activity can be considered as a prognostic factor in cancer. Despite these common

factors and mechanisms, the majority of the literature mainly focused on HRV and cancer prognosis, leaving its role in cancer onset under-examined.

Therefore, we explored the predictive role of HRV in cancer onset (Study 1), and found that HRV was indeed a predictor of cancer onset, but only in people over 40 years old. Additionally, several studies suggest a moderating role of vagal nerve activity concerning other risk factors. Thus, we also examined the moderating role of vagal nerve activity in the relationship between life-threatening events (LTE) and cancer onset (Study 2). We found that LTE predicted cancer-onset only in people with initially low HRV, thus, vagal nerve activity is a protective factor against the effect of LTE on cancer onset. Those results suggest that vagal nerve activity could actually be a therapeutic target in order to prevent cancer. Breathing exercises increase HRV. However, due to contradictory results on breathing techniques, conducted an experimental study to examine the effects of different breathing exercises on HRV by manipulating breathing frequency and pattern. Though all conditions increased HRV, the efficacy of breathing exercises depended on their breathing frequency. Indeed, while every frequency (0.1, 0.08 and 0.07 Hz) led to significant increases in HRV, the largest increase was found for 0.08 Hz, for RMSSD and for both 0.08 and 0.07 Hz for LF-HRV.

These results contribute theoretically to the domain of neuromodulation of diseases by revealing the predictive and protective roles of the vagal nerve in cancer-onset. These results also have clinical implications for public health by using HRV as a marker of cancer risk. This can serve cancer prevention and management since vagal activity can be a therapeutic target.

Keywords: cancer, vagal nerve, heart rate variability, psychological factors, psychophysiology

RESUME

L'objectif général de cette thèse était de comprendre le rôle du nerf vague dans l'apparition du cancer et de caractériser sa relation avec les facteurs de risque de cancer. Dans le premier chapitre de cette thèse, nous avons présenté comment des facteurs psychologiques, liés à la fois à la santé mentale et aux comportements de santé, pouvaient influencer le développement du cancer. En effet, le stress chronique (résultant de la dépression, de l'anxiété ou d'événements de vie) peut activer le système nerveux sympathique, l'axe hypothalamo-hypophyso-surrénalien (HHS) et affecter le système immunitaire et l'inflammation. Ces mécanismes sont également impliqués dans le développement du cancer. De la même façon, nous avons expliqué comment les comportements de santé influencent les mécanismes biologiques impliqués dans le développement du cancer, de la mutagenèse à la métastase.

Cette thèse s'est concentrée sur le rôle du nerf vague, le deuxième chapitre présente le nerf vague ainsi que ses associations aux facteurs psychologiques de risque et de pronostic, ainsi qu'au pronostic du cancer. En effet, des valeurs plus faibles de variabilité du rythme cardiaque (VRC), l'indice vagal, sont associées à des facteurs de risque et de pronostic tels que la dépression, l'anxiété, la consommation d'alcool ou une faible activité physique. De plus, le nerf vague est un élément clé de l'axe neuro-immunitaire, qui est impliqué dans la régulation de la réponse sympathique et inflammatoire (toutes deux impliquées dans le développement du cancer). Enfin, la VRC a un rôle pronostique dans la survie au cancer. En conclusion, le nerf vague est lié aux facteurs de risque de cancer, à la régulation des processus impliqués dans le développement du cancer et l'activité vagale peut être considérée comme un facteur pronostique du cancer. Malgré ces facteurs et mécanismes communs, la majorité de la littérature s'est principalement concentrée sur la VRC et le pronostic du cancer, laissant son rôle dans l'apparition du cancer sous-examiné.

Nous avons exploré le rôle prédictif de la VRC dans l'apparition du cancer (Etude 1) et avons constaté que le VRC était effectivement un facteur prédictif de l'apparition du cancer, mais uniquement chez les personnes de plus de 40 ans. De plus, plusieurs études suggèrent un rôle modérateur de l'activité du nerf vague. Ainsi, nous avons examiné le rôle modérateur de la VRC dans la relation entre les événements de vie (EV) et l'apparition du cancer (étude 2). Nous avons constaté que les EV prédisaient l'apparition du cancer uniquement chez les personnes dont le VRC était initialement faible. Ainsi, l'activité du nerf vague est un facteur de protection contre l'effet des EV sur l'apparition du cancer. Ces résultats suggèrent que l'activité du nerf vagal pourrait être une cible thérapeutique afin de prévenir le cancer. L'une des possibilités pour augmenter la VRC est de réaliser des exercices de respiration. Cependant, en raison de résultats contradictoires concernant leur efficacité, nous avons mené une étude afin d'examiner les effets de différents schémas respiratoires sur la VRC en manipulant la fréquence et le schéma des exercices. Bien que toutes les conditions permettent une augmentation de la VRC, l'efficacité des exercices dépend de leur fréquence respiratoire. En effet, bien que les trois fréquences (0,1, 0,08 et 0,07 Hz) entrainent une augmentation significative de HRV, la plus importante est obtenue avec la fréquence de 0,08 Hz.

Ces résultats contribuent au domaine de la neuro-modulation des maladies en révélant les rôles prédictifs et protecteurs du nerf vague dans l'apparition du cancer. Leurs implications cliniques pour la santé publique en utilisant la VRC permettrait d'améliorer la prévention et à la gestion du cancer puisque l'activité vagale peut être une cible thérapeutique.

Mots clés : Cancer, nerf vague, variabilité du rythme cardiaque, facteurs psychologiques, psychophysiologie

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INTRODUCTION

Worldwide, the International Agency for Research on Cancer (IARC) estimates over 19 million new cases of cancer in 2020. As addressed in more detail in the first chapter, cancer as a multifactorial disease results from the interaction between several risk factors. For the World Health Organization (WHO), between 30 and 50% of those cancers can be prevented by limiting preventable risk factors and implementing prevention strategies. Similarly, understanding prognostic factors is crucial to reduce mortality. In fact, the IARC estimated that cancer still caused up to 10 million deaths in 2020. Although significant progress has been made in preventing the disease and taking care of patients, cancer remains one of the leading causes of death and disability in the world (WHO, 2020).

As a multifactorial disease, cancer results from the interaction of several factors, such as psychological, environmental or genetic factors. This contributes to the complexity of cancer prevention. In order to understand this complexity and to be able to identify a common factor, we focused on the vagal nerve and investigated the relationship between vagal nerve activity cancer risk.

In order to explain why this thesis is interested in the vagal nerve and its relation to cancer, the first part, the theoretical introduction, will consist of three chapters. The first one introduces basic biological mechanisms leading to the development of cancer, risk and prognostic factors and the relationship between those factors and cancer development. The second chapter will concern the vagal nerve, its activity and its relationship with cancer development and cancer risk and prognostic factors. Finally, the last chapter will present the rationale, objectives and hypotheses of this thesis.

The second part of this thesis will be empirical and will include presentation of studies in article formats: The first two are database analyses and the last chapter is an original experimental study. The first one highlights the predicting role of vagal nerve activity in cancer onset, the second one highlight the moderating role of vagal nerve activity between life- threatening events and cancer onset. Finally, the last chapter is a comparative study of several breathing exercises aimed at increasing vagal nerve activity.

The final part of the thesis will be the general discussion. We will first summarize the main findings, and then we will discuss the results of these studies, meaning address their limitations and have a comprehensive discussion of our results in order to clarify them and highlight their contributions. Then, we will propose a model to illustrate the relationships between psychological factors and cancer. Finally, we will develop our future directions.

THEORETICAL PART

CHAPTER 1 - CANCER

This first chapter aims to introduce cancer development. Biologicals mechanisms of cancer development will be briefly explained in the first part, then, psychological risk and prognostic factors which influence cancer development will be presented. Finally, the relationship between those factors and biological mechanisms will be explained. The objective of this chapter is to highlight the biological pathways by which psychological risk and prognostic factors influence cancer development (see Figure 1).

Figure 1: Linear model of the relationship between psychological factors on cancer

1. BIOLOGY OF CANCER

From a biological point of view, cancer is a group of diseases characterized by abnormal and uncontrolled cellular growth caused primarily by genetic mutations (Stratton et al., 2009). Cancer development is a complex multi-step process (see Figure 2), which could be divided into three phases: initiation, promotion and progression (Miguel Guamán-Ortiz, 2018). Initiation is the early stage, characterized by *mutagenesis* and *carcinogenesis* by which normal cells undergo mutations and turn into cancerous cells. Then, promotion is the process of tumor growth, and during this stage cancerous cells form a tumor (i.e., *neoplasm*) and develop blood vessels (i.e., *angiogenesis*). Finally, the later stage of cancer, progression, involves *metastasis*, where the tumor becomes invasive and spreads to distant locations in the body. In addition, the promotion and progression require a favorable microenvironment, called the *tumor microenvironment*. This microenvironment ensures communication between the tumor and the biological systems necessary for *angiogenesis* and *metastasis*: the immune and nervous systems. For the sake of clarity, in this thesis,

cancer development will be used to refer to any of those phases and processes whenever more precise information will not be necessary.

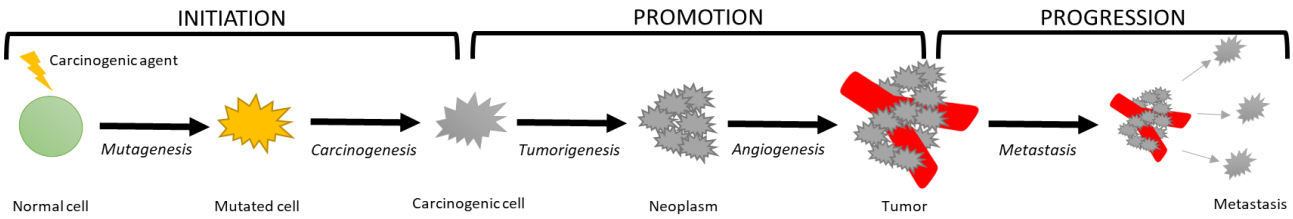

Figure 2: Cancer development

Important elements of cancer development are explained in the next sections, following their chronological order of occurrence. In the first part, genetic mutations, cellular growth and the tumor microenvironment will be presented. The second part will focus on the role of the immune and the nervous systems in cancer development.

1.1. GENETIC MUTATION

A genetic mutation (or DNA mutation) is a permanent alteration in the sequence of one gene. They can be either inborn or acquired. Those mutations will affect the gene expression. Cells are constantly undergoing DNA mutations induced by aging, dysfunction of cellular mechanisms (i.e., *oxidative stress*) or exposure to mutagenic agent, but fortunately, DNA repair mechanisms are able to repair most of them. Thus, not every mutation will lead to cancer. Indeed, in order to induce a cell to transform into a carcinogenic cell (a mutated cell, which will become a cancer), those mutations have to affect genes associated with cancer (i.e., cancer-genes) in a specific way. Cancer-genes and the mutation leading to cancer may be categorized as following:

Oncogenes and proto-oncogenes: genes that are involved in cellular growth promotion. A mutation on those genes and an increase in their expression will induce an increased cell proliferation.

Anti-oncogenes: genes that are involved in inhibition of cell proliferation and in tumor suppressor processes. A mutation in those genes, making them defective, will prevent the inhibition of cell proliferation and suppression of carcinogenic cells, which will lead to an increased cell proliferation and carcinogenic cells' accumulation.

Apoptotic genes: genes that are involved in programmed cell death (i.e., *apoptosis*). A mutation in those genes will make them defective; cells will not undergo apoptosis, leading to carcinogenic cells' proliferation and accumulation.

Anti-apoptotic genes: genes that are involved in inhibition of *apoptosis*. A mutation in those genes, leading to an increase in their expression, will prevent apoptosis, and will lead to carcinogenic cells' accumulation.

The human genome contains approximately 120,000 genes (Liang et al., 2000), and the Integrative OncoGenomics (IntOGen) pipeline lists 568 cancer-genes which may suffer from more than 203,000,000 different mutations which can lead to 66 cancer types. For example, 99 genes can carry mutations that increase the risk of developing breast cancer (Martínez-Jiménez et al., 2020). Mutations can be either inborn or acquired. Inborn mutations are passed on to children from their parents, most famous being Breast Cancer (BRCA) genes mutations, involved in “familial breast cancer”. On the other hand, acquired mutations are the result of mutagenic agents or biological processes such as oxidative stress (Valko et al., 2004). However, not all mutagenic agents are able to induce mutations that will lead to *mutagenesis* and cancer; those able to do it are called *carcinogenic agents* or *carcinogens.*

In conclusion, to induce cancer, genetic mutations must appear on cancer-genes, whether inborn or acquired because of a *carcinogen*. Those mutations will affect cellular growth regulation, allowing cells to mutate and proliferate.

1.2. CELLULAR GROWTH

Cellular growth is a normal process by which cells multiply. As this process is complex, it will not be explained in detail. However, it is necessary to address that it involves cell multiplication but also many control processes in order to keep an equilibrium called *cellular homeostasis* between cell growth and death. Normal cellular growth implies several checkpoints, control and repair mechanisms. Cells are able to limit their own proliferation, make DNA repair or even go through *apoptosis* (self-destruction). When mutation appears, which makes the cell dangerous or simply ineffective, that mutated cell will undergo repairs process or an elimination process via apoptosis, thus, it will not proliferate with mutation (see Figure 3).

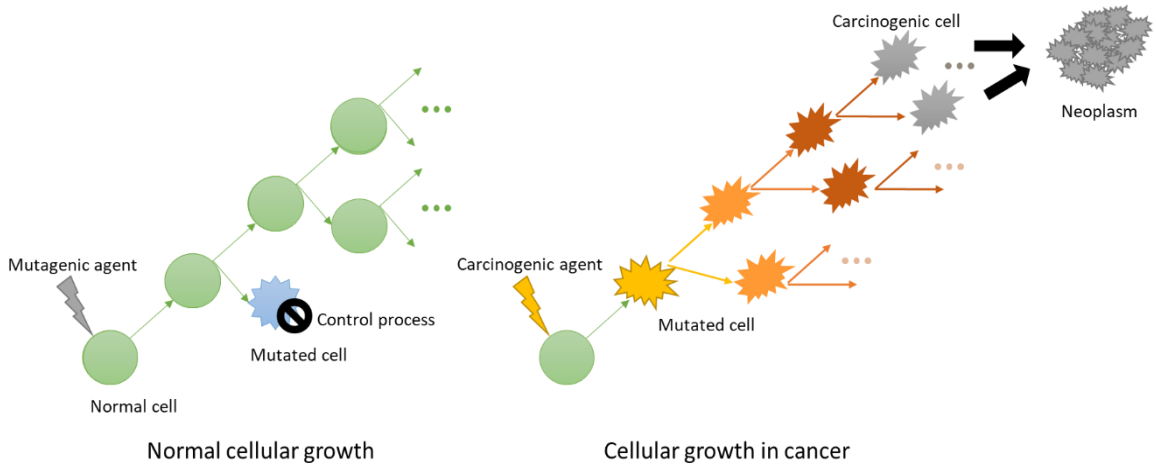

Figure 3: Cellular growth

Cellular growth is involved in the development of cancer at several stages, from *carcinogenesis* through *tumorigenesis* and *metastasis*. In cancer, as explained above, mutations will occur in cancer-genes coding for cellular growth control mechanisms, hence, the cellular growth of the mutated cell occurs without control. It will then multiply several

times, which leads to more mutations of cancer-genes, until this normal cell becomes a carcinogenic cell. It is the first step: *carcinogenesis,* a normal cell becomes a carcinogenic cell. Then, those carcinogenic cells will multiply without control and form a neoplasm (a group of mutated cancer cells); it is the *tumorigenesis*. Finally, when cancer cells spread and settle in another tissue, cell growth will lead to the formation of a new tumor, it is the last stage: *metastasis*. Metastasis is responsible for the majority of cancer deaths (Dillekås et al., 2019).

Last, cellular growth is involved in several stages of cancer development. However, once the tumor has formed, in order to proceed through the overall process of development, the tumor also needs a favorable environment and it is the main role of the tumor microenvironment.

1.3. TUMOR AND TUMOR MICROENVIRONMENT

Creating adequate conditions for the growth and sustainability of tumors is the role of the tumor microenvironment (TME). Tumor cells stimulate significant molecular, cellular and physical changes within their host tissues to support tumor growth and progression: the tumor shapes its microenvironment. Thus, the composition of the TME varies between tumor types and tumors' needs. It is a complex and continuously evolving entity which regulates essential tumor survival and promotion functions. It allows cancer cells to become invasive, to spread and to settle down in a secondary location (*metastasis*). Indeed, due to the TME, the tumor is able to grow vessels (*angiogenesis*) and nerves (*innervation or neoneugenesis*) which are both required for cancer progression. Those new vessels and nerves are then an integral part of the TME and will play an important role in the crosstalk between nerves, the immune system and cancer cells (Anderson & Simon, 2020; Neophytou et al., 2021; H. Wang et al., 2021).

In recent years, the concept of cancer biology has shifted from studying the genetics of tumor cells alone to the field of the complicated interplay between tumor cells and the TME as an interface between the tumor and the rest of the body.

At this point, the process by which a normal cell may become a carcinogenic cell and then a tumor is a bit clearer. Cancer starts with a normal cell that suffers from genetic mutations in cancer genes, allowing them to escape control mechanisms and undergo pathological cellular growth. The tumor will then shape its microenvironment in order to pursue its progression. However, those cells are part of a more complex, multilevel system: the human body. Beyond molecular (DNA repairs) and cellular (cellular growth) control mechanisms, the roles of the immune system and of the nervous system in cancer regulation need to be addressed. Those biological systems and their involvement in cancer development will be the focus of the next section.

2. BIOLOGICAL SYSTEMS AND CANCER DEVELOPMENT

2.1. THE SYMPATHETIC NERVOUS SYSTEM

The implication of the sympathetic nervous system in cancer development has been established for a variety of cancers. For example, in breast cancer, tumor growth and progression increase following stimulation of sympathetic nerves (Kamiya et al., 2019). Moreover, ablation of sympathetic nerves inhibits tumorigenesis in prostate cancer (Magnon et al., 2013). Indeed, adrenergic neurotransmitters (epinephrine and norepinephrine), which are specific to the sympathetic system, are involved in the regulation of numerous cancer related processes including inflammation, angiogenesis, apoptosis or immune responses (e.g., Ağaç et al., 2018; Xanthopoulos et al., 2021). The sympathetic activation enhances cancer development by stimulating inflammation and inhibiting anti-inflammatory processes on one hand (Cole et al., 2015) and inhibiting anti-

cancer immunity on the other hand (Capellino et al., 2020; Cole et al., 2015). Indeed, adrenergic signaling can inhibit DNA damage repairs, downregulate apoptosis, modulate growth and survival pathways, and activate a range of cells present in the TME (Cole et al., 2015). Moreover, increased adrenergic stimulation can impair response to chemotherapy (Kang et al., 2016).

Accordingly, many studies explored the impact of adrenergic antagonists on cancer. As antagonist, beta blockers prevent the effect of adrenergic neurotransmitters, which lead to reduced metastases and increased survival (e.g., Choy et al., 2016; Watkins et al., 2015). These findings clearly show causal effects and the cellular and immunological mechanisms of sympathetic activation in tumorigenesis.

2.2. THE IMMUNE SYSTEM AND INFLAMMATION

The immune system[1] is based on the principle of self and non-self-recognition: everything that cannot be recognized as part of self may be destroyed. Those non-self-elements (e.g., viruses, parasites or bacteria) are usually regrouped under the term *pathogens*. Their recognition by immune cells uses signals (i.e., *antigens, major histocompatibility complex MHC)* expressed at the surface of most cells. Those signals will inform immune cells if a cell is part of self or not, and if an immune response is needed. In order to elicit immune responses, antigens need to be *immunogenic:* non-self-antigens are immunogenic, thus they induce an immune response. The immune response may involve either the innate or the acquired immune system. The innate response will deal with every immunogenic pathogen; the acquired immune response will deal with pathogens that have been encountered in the past (Delves & Roitt, 2000).

1 Elements reported in this section are mainly taken from the book *Immunologie* (Kuby et al., 2014). Thus, for the sake of clarity, only the references of the elements not taken from this manual will be indicated.

With respect to cancer, the immune system can act at several steps of cancer development. The first point is before *mutagenesis* by eliminating carcinogenic pathogens. In fact, several cancers are associated with pathogens (e.g., viruses). Those pathogens will induce *mutagenesis* and lead to abnormal cell growth and cancer development (Hatta et al., 2021). The most famous example is certainly the cervical cancer induced by the Human Papillomavirus (HPV). In order to prevent this cancer, a vaccine has been developed to reduce cervical cancer incidence (Lei et al., 2020). Indeed, this vaccine allows the development of acquired immune responses against HPV. Secondly, the immune system could act after *mutagenesis* by eliminating mutated, carcinogenic or tumor cells, this is the anti-cancer immune response. However, from an immunological point of view, cancer cells are self-cells; they are self-cells which underwent mutations and have escaped the various regulatory mechanisms. One such escape mechanism is their reduced expression of MHC-I, thus escaping elimination by *cytotoxic T-cells*. Thus, it will be more difficult for the immune system to identify and eliminate those cells. Nevertheless, there is an anti-cancer immunity based on the lack of MHC at the surface of cancer cells – via n*atural killer NK-cells.* These cells identify the tumor cells as non-self-cells and can elicit an anti-cancer immune response (Liu et al., 2021).

The immune response regardless of its target induces an inflammation. This inflammation mostly consists of the innate immune response; it refers to the recruitment of immune cells (inflammatory cells and cytokines). Although this reaction is normal and beneficial when this reaction is acute and lasts for a few hours or days, it becomes problematic when the inflammation lasts for weeks, months or even years. Indeed, it happens that the body and immune system continue to send inflammatory cells for an extended period, which leads to chronic inflammation. The risk to suffer from chronic inflammation increases with age, obesity, poor diet, smoking, chronic stress and sleep

disorders. Finally, chronic inflammation is associated with numerous chronic diseases such as cancer, Alzheimer's disease, heart disease, type 2 diabetes and rheumatoid arthritis (Pahwa et al., 2021).

With respect to cancer, chronic inflammation promotes escape from apoptosis by inhibiting tumor suppressors at early stages (*carcinogenesis*), and promotes *angiogenesis* and *metastasis* at later stages (Mantovani et al., 2008; Voronov et al., 2003). In fact, the tumor redirects all immune and inflammatory processes to its benefit. The tumor can either promote the immune response and inflammation or inhibit immune responses and inflammation in its microenvironment, depending on its needs. Thus, the tumor inhibits immune responses by releasing anti-inflammatory cytokines (i.e., *IL-10*) or by producing *TGF-β* which inhibits anti-cancer immunity, in order to protect *tumorigenesis*. But the tumor also promotes inflammation to divert repairs process and molecules such as *cytokines* (e.g., *IL-1*, *IL6*) or *growth factors* (e.g., *VEGF*) in order to create new blood vessels (*angiogenesis*) and increase vascular permeability, which allows the spreading (*metastasis*) (e.g. H. Zhao et al., 2021).

The first section of this chapter presented the mechanisms involved in cancer development. From the normal cell undergoing genetic mutation to the implication of the immune and nervous systems, we highlighted the biological complexity of cancer development and the importance of the neuro-immune axis in cancer development.

Furthermore, as mentioned at the beginning of this thesis, cancer is a multifactorial disease, resulting from the interaction of several factors. Those factors are risk and prognostic factors and they influence biological mechanisms detailed in this section. Risk and prognostic factors are the subject of the next section.

3. CANCER RISK AND PROGNOSTIC FACTORS

Each case of cancer is unique, and each person may have a different combination of risk factors that will lead to the development of cancer. Similarly, the prognosis of patients will depend on many prognostic factors both specific to the disease and to the patient. In fact, cancer as a multifactorial disease, which results from the interaction of several factors. Those factors are any variable that increases the likelihood of developing a disease (risk factor) or influences the prognosis of a patient (prognostic factor).

This section will present briefly environmental factors and then focus on psychological ones and the identified underlying mechanisms by which they influence cancer development and prognosis.

3.1. ENVIRONMENTAL RISK FACTORS

Although this thesis does not focus on environmental factors, it seems important to highlight their role in cancer onset. The International Agency for Research on Cancer (IARC) classified around 100 compounds as being carcinogenic (i.e., able to induce genetic mutations on cancer-genes), most of them being environmental (e.g., radiation, pesticides, asbestos, smoke) (Sankpal et al., 2012). This “pollution” is everywhere: in the air, food or even in clothes. For example, the risk of lung cancer for people exposed to asbestos was doubled compared to unexposed people, and a cumulative asbestos exposure of 10 years or more multiplies the risk by three (Suraya et al., 2020). Secondhand smoking is considered as an environmental risk factor which increase the risk of oral cancer (Mariano et al., 2022).

Thus, environmental *carcinogens* are risk factors. Regarding the role of such agents on prognosis, it seems that there are fewer studies focusing on this aspect. However, a recent article highlighted that they may be involved in treatment resistance through several pathways, one of them being a modification in the TME (Lagunas-Rangel et al., 2022).

Resistance to treatment reduces the effectiveness of a treatment, which may lead to worse prognosis. For example, bisphenol A, which is used as a compound of plastic is associated with chemoresistance (i.e., resistance to chemotherapy) in breast cancer patients (LaPensee et al., 2009).

3.2. PSYCHOLOGICAL FACTORS

The interest in the prognostic role of psychological factors in cancer is relatively recent. The interest in the role of psychological factors in cancer started with the psychological impact of having cancer, and then gradually this interest shifted to the study of the effects of psychological factors on cancer risk and prognosis.

Psychological factors refer to emotional, cognitive and behavioral aspects of a person. In this section, the role of several psychological factors in cancer risk and prognosis will be presented. We will examine the impact of life events, psychological distress, depression, anxiety and finally of health behaviors in cancer risk and prognosis.

3.2.1.Life events

For decades, clinicians and patients have speculated that life events and psychological factors may put people at risk for developing cancer (Spada et al., 2022). In the literature, those life events refer to either traumatic life events, major stressful life events, striking life events, or life-threatening events. They generally consist of changes in marital status (e.g., separation, divorce, and widowhood), death of a close relative (e.g., spouse/husband, child, parent, and siblings), illness of a close relative/friend, personal health problems, financial problems or unemployment.

The original research to evaluate life events dates back to Holmes and Rahe (1967). The authors wished to provide a method for clarifying the relationship between sociological, psychological, and biological factors involved in the process of health and

disease (Holmes & Rahe, 1967). Since then, numerous research has explored the relationship between life events and cancer onset and some studies did show that life events were related to a higher risk of developing cancer. For instance, the risk estimation to have breast cancer increases with divorce/separation or death of a husband but also with the total number of life events is supported by several case control studies but also prospective studies and meta-analysis (Bahri et al., 2019; Lillberg et al., 2003; Y. Lin et al., 2013, 2017). Accordingly to case-control studies, life events are also a risk factor for colorectal cancer (Azizi & Esmaeili, 2015) and lung cancer (Jafri et al., 2019).

Regarding the role of life events in cancer prognosis, the literature is less abundant than for cancer onset, however, a few studies show that life events may have no effect on prognosis (e.g., Maunsell et al., 2001; Olsen et al., 2012).

3.2.2.Psychological distress, depression, and anxiety

Regarding the role of psychological factors in cancer, depression, anxiety and, more generally, psychological distress are by far the most studied factors. In fact, depression and anxiety feature as leading mental health issues worldwide. The prevalence is around 5% for both depression and anxiety (Institute for Health Metrics and Evaluation, 2019). Although the prevalence differs between studies, the prevalence among cancer patients remains significantly higher than among the general population, independently of cancer location, age, sex or any other demographic variable. All cancers combined, 48% of patients suffer from depression and 46% from anxiety (Nikbakhsh et al., 2014). Looking at certain types of cancer, 32% of women with breast cancer suffered from depression (Pilevarzadeh et al., 2019) while 43% of lung cancer patients have anxiety and 57% of them have depression (Yan et al., 2019). Concerning psychological distress (i.e., a set of

symptoms of depression and anxiety), it affected 33% of gastric cancer patients (G. M. Kim et al., 2017).

Recently, several studies have highlighted the relationship between depression and cancer (Y.-H. Chen & Lin, 2011; A. L. Gross et al., 2010; Jia et al., 2017). For example, Gross and collaborators found that depression multiplies by two the risk of all cancers and by four the risk of breast cancer. A recent meta-analysis highlights that clinical diagnosis of depression and anxiety are associated with an increased risk of cancer onset, but also mortality in cancer patients (Y. H. Wang et al., 2020). This study also looked at psychological distress and found that higher levels of distress are related to a higher cancer-specific mortality and to poorer cancer survival (but not to increased cancer onset).

3.2.3.Mechanisms by which psychological factors influence cancer development

Distress, depression, anxiety or life events are usually reported as "*stress*". Behind this stress, one refers to event(s) or situation(s), which have affected people's wellbeing. Stress may be defined as the response of an organism to external, physiological or psychological stimuli, which exert effects on the molecular, cellular, organ and psychological level (Hong et al., 2021). Chronic stress activates the neuroendocrine system: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) which increase cancer onset. In addition, chronic stress also affects the immune function of the body, leading to the decline of immune monitoring ability and inhibition of anti-tumor immunity on one hand, and increased inflammation on the other hand (Hong et al., 2021). A growing body of research has shown that there is a link between chronic stress and tumor occurrence in both animal studies and clinical studies (Bu et al., 2020; H. Chen et al., 2018; X. H. Lin et al., 2020; Saul et al., 2005; Zhang et al., 2019). Moreover, there is direct experimental evidence that stress hormones can enhance the invasive potential of ovarian

cancer cells. (Sood et al., 2006). Similarly, depressive disorders induce HPA axis and sympathetic nervous system activation, suppression of immune cell surveillance, chronic inflammation which are likely responsible for accelerated cancer burden (Bunimovich et al., 2022). Moreover, depression and anxiety are both associated with increased oxidative stress and inflammation (Patki et al., 2013), both involved in cancer development.

3.3. HEALTH BEHAVIORS

Health behaviors are defined as any activities undertaken by individuals for the purpose of maintaining, enhancing, or protecting their health (Gochman, 1997). According to Kasl & Cobb (1966), we can classify health behaviors in three categories based on their purpose: to maintain good health, to cure the illness and to get better. In contrast, unhealthy behaviors are associated with a higher risk of poor health. The effects of health behaviors such as smoking, drinking, having a healthy diet, or regular physical activity, are now well established. This section presents behavioral factors involved or potentially involved in the development and prognosis of cancer.

Unhealthy behaviors such as alcohol consumption, tobacco use, low fruit and vegetable intake, and lack of physical activity are responsible for one-third of cancers (World Health Organization, 2022). Indeed 42% of all incident cancers and 45% of cancer deaths were attributed to those risk factors (Islami et al., 2018).

3.3.1.Alcohol and tobacco

Alcohol is a leading risk factor. It increases the risk of developing several cancers such as oral cavity, pharynx, esophagus, colorectal, liver, larynx, breast, pancreas, prostate cancer, and melanoma (Bagnardi et al., 2015; Rehm et al., 2020). The role of alcohol in patients' prognosis is less clear. Indeed, some studies suggested that heavy consumption is associated with poorer survival, for example in colorectal cancer (Walter et al., 2016),

whereas other studies did not find any association with survival or recurrence in breast cancer patients (Kwan et al., 2013). However, patients who struggle with alcohol will often have impaired medical surveillance, which leads to a late diagnosis, associated with poorer prognosis (Schütte et al., 2012).

The role of smoking is well established for both cancer risk and prognosis. For example smoking increases risk of lung cancer (O'Keeffe et al., 2018), bladder cancer (Hou et al., 2017), breast cancer (Fentiman et al., 2005) and colorectal cancer (Ordóñez-Mena et al., 2018). In the latter study, the authors showed that former and current smokers had a poorer prognosis compared with patients who never smoked. Moreover, smoking cessation has been associated with fewer complications, less recurrence and increased survival (Warren et al., 2014). Moreover, quitters are less depressed and have a better quality of life after the treatment (Martínez et al., 2019).

The mechanisms by which alcohol and tobacco may influence the development of cancer are not fully understood. However, what is known is that alcohol and tobacco are carcinogens capable of inducing mutations in cancer genes, which explains how it increases cancer risk. In addition, heavy alcohol and tobacco consumption induce chronic inflammation that is implicated in several stages of cancer development (e.g., Rumgay et al., 2021). Moreover, tobacco is well known to induce oxidative stress. Oxidative stress refers to elevated intracellular levels of reactive oxygen species (ROS) that cause damage to lipids, proteins and DNA, leading to mutations (Schieber & Chandel, 2014).

3.3.2.Diet and physical activity

When it comes to diet, scientists have suspected for decades that nutrition has an important influence on health. Even if there are numerous recommendations (e.g., American Institute for Cancer Research, American Cancer Society), they all emphasis

similar aspects such as eating vegetables and fruits each day, to limit processed food, sugar, or fat (e.g., Guenther et al., 2013; Rock et al., 2020; Willett et al., 1995). In respect to cancer, several studies and more recently a meta-analysis showed that an unhealthy diet indeed led to increased risks of cancer for example in colorectal cancer (Zheng et al., 2021), whereas a healthy diet which is defined as a balanced and varied diet, lowered the risk of cancer mortality (Morze et al., 2021). It is difficult to understand how nutrition acts, however, there are some carcinogenic agents known to be found in food. Hence, it is not food itself, rather what it contains, which can be either carcinogenic or pro-inflammatory. A recent review about food and cancer prevention highlight that even if dietary intake accounts for an important part of several cancer, such as colorectal, breast or gastric cancer, they have not yet been comprehensively investigated (Xia et al., 2022).

Finally, physical activity is associated with reduced risk of cancer and improved prognosis of several cancers (Behrens et al., 2014; Chen et al., 2019; Mctiernan et al., 2019), while in contrast, sedentary behavior (low physical activity) is associated with an increased risk of cancer (Jochem et al., 2019). In order to clarify, physical activity includes sportive activity, professional activity, recreational activity, or even transportation mode and having more than 150 minutes of moderate-intensity physical activity per week, before diagnosis and/or after cancer treatment. Physical activity above that amount appears to be associated with reduced recurrence and mortality among breast cancer patients (Cannioto et al., 2021). Regarding how physical activity may influence cancer onset and prognosis, we may refer to a direct and an indirect effect. The indirect effect would be by reducing diabetes, high blood pressure, or body mass index (e.g., Jakicic, 2009; Jeon et al., 2007; Kokkinos et al., 2009) which are known cancer risk factors (H. Han et al., 2017; Lega & Lipscombe, 2020). From a biological point of view, there are several possible biological mechanisms through which physical activity could affect cancer risk and prognosis, among

them the reduction of systemic inflammation by improving anti-inflammatory response (Ferrer et al., 2018) or reducing oxidative stress (Meijer et al., 2002).

When trying to understand how emotional psychological factors and health behaviors can have a biological influence on cancer development, there are many mechanisms involved. First, some of them have a clear effect on mutagenesis, because they are associated to *carcinogens* (e.g., alcohol, tobacco or pesticides in food). Other are mostly related to chronic stress (e.g., depression, anxiety or life events) which activates the neuroendocrine system (hypothalamic-pituitary-adrena axis and the sympathetic nervous system) and the immune system. Finally, as illustrated by physical activity, they may have be involve in cancer development though many pathways like oxidative stress or inflammation but also more indirect pathways like reducing the occurrence of other risk factors. This actually highlight the complex interplay between risk factors, which participate to the complexity of cancer prevention.

CHAPTER 2 – THE VAGAL NERVE

The interest in the vagal nerve comes from its involvement in the regulation of mechanisms, which promote tumor development (e.g., inflammation), from its relationship with risk and prognostic factors (e.g., diet) and from its ability to predict patient prognosis and survival. The aim of this chapter is to present each of those elements.

The first section of this chapter will introduce the vagal nerve. For pedagogical purposes, the first section starts with a brief reminder of the neuroanatomy of the nervous system in order to situate the vagal nerve in the overall system. The second section will present the role of the vagal nerve in the regulation of inflammation, sympathetic activity and stress response. The third section will focus on the measurement of the vagal nerve activity. Finally, even if some mechanisms are still unclear, the last section will present what is already known regarding the relationship between the vagal nerve and cancer.

1. INTRODUCING THE VAGAL NERVE

1.1. GENERAL NEURO ANATOMY OF THE NERVOUS SYSTEM

The nervous system[2] (NS) is responsible for the analysis of external and internal stimuli and allows maintaining of the organism's homeostasis. It is composed of the central NS (CNS) and the peripheral NS (PNS) (see figure 4). On one hand, the CNS is in charge of the analysis of external and internal stimuli, their integration, and the decision-making process. It is composed of the encephalon (cerebrum, cerebellum and brainstem) and the spinal cord. On the other hand, the PNS connects the CNS with the rest of the body, and is

[2] Elements reported in this section are mainly taken from the book *Neuroanatomie* (Crossman et al., 2004). Thus, for the sake of clarity, only the references of the elements not taken from this manual will be indicated.

composed of cranial and spinal nerves. The cranial nerves have their origin in the encephalon while the spinal nerves have their origin in the spinal cord.

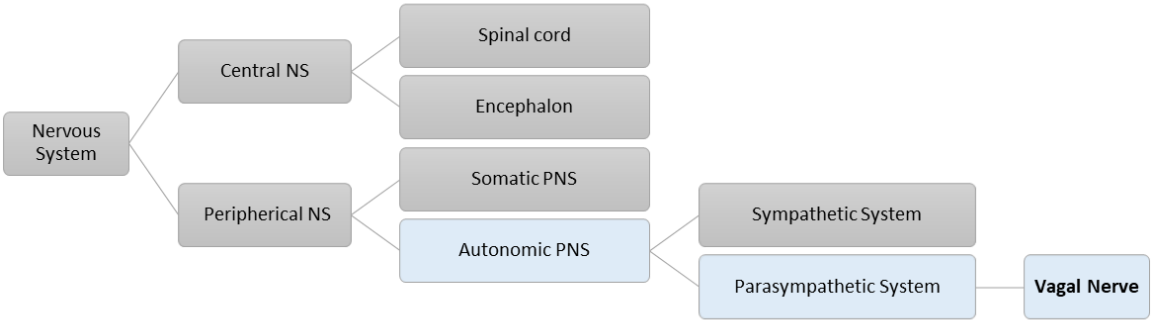

Figure 4: The nervous system

The somatic branch of the PNS is in charge of the interaction with the environment (motor and sensory systems) and is associated with voluntary control of the body movements (e.g., walking). In contrast, the autonomic branch of the PNS (ANS) oversees the control and regulation of biological functions and is associated with involuntary movement (e.g., breathing). The somatic branch underlines the conscious and voluntary activity (e.g., running) while the ANS is responsible for the unconscious activity (e.g., breathing and heart rate).

The ANS coordinates and controls the functioning of the internal organs and is thus responsible for all the automatic functions, namely the respiratory, digestive, and cardiovascular systems. It acts on the smooth motility of the internal organs, the vasomotricity and the visceral secretions of the exocrine and endocrine glands. The ANS, in coordination with the endocrine and the immune systems, is involved in body homeostasis. The regulatory function of the ANS is possible thanks to its two antagonistic and complementary branches. The sympathetic system participates in the alert reaction while the parasympathetic system allows a return to normal after an alert. Their mutual activities provide the autonomic balance. The SNS and PNS are under control of the central

autonomic network (CAN), a group of brain regions (e.g., insular cortex, amygdala, hypothalamus, nucleus tractus solitarius).

One of the most important nerves of the parasympathetic system is the vagal nerve; in fact, it is the longest nerve in the body and has a wide distribution as it is involved in the parasympathetic innervation of multiple visceral organs such as the heart, pancreas, lungs, and gastrointestinal tract. Initially, the vagal nerve was considered as an efferent nerve, composed exclusively of efferent fibers (i.e., carry information *from the* CNS, "top-down"). However, in 1938, Bailey and Bremer found that vagal nerve stimulation induced changes in heart rate, suggesting the presence of afferent fibers (i.e., carry information *to the* CNS, "bottom-up") (Bailey & Bremer, 1938). The vagal nerve is now considered as a mixed nerve: 20% of its fibers are efferent, while 80% of its fibers are afferent. Thus, the vagal nerve can transfer bidirectional signals between peripheral organs and the CNS.

1.2. THE VAGAL NERVE AND THE NEURO-IMMUNE AXIS

The vagal nerve is a key component of the neuro-immune axis; indeed, as a parasympathetic nerve it is involved in the regulation of both sympathetic activity and the immune system.

The vagal nerve regulates the sympathetic activity at two levels. On one hand, as part of the parasympathetic system, the vagal nerve is involved in the global autonomic balance and thus in the regulation of sympathetic activity. On the other hand, the vagal nerve can regulate the sympathetic system via a specific connection: the vago-sympathetic pathway. This pathway involves the CAN, i.e. a structure located in the CNS, composed among others structures of the nucleus tractus solitarius and the amygdala, which are at the origin of the autonomic response. Thus, the afferent vagal fibers modulate sympathetic activity

and this gives the vagal nerve the ability to regulate many mechanisms linked to sympathetic activity, such as inflammation and stress responses (Bonaz et al., 2017).

The vagal nerve is also involved in the regulation of inflammation through the hypothalamic-pituitary-adrenal (HPA) axis and the cholinergic anti-inflammatory pathway (CAP). Specifically, the vagal nerve is sensitive to peripheral pro-inflammatory cytokines, such as interleukin (IL)-1, Il-6 and tumor necrosis factor alpha (TNFα), that are released by macrophages and other immune cells. After the activation of the afferent vagal fibers by cytokines, there is an activation of the nucleus tractus solitarius, which will then induce the activation of the HPA axis leading to the release of glucocorticoids (e.g., cortisol) by the adrenal glands. These hormones will then inhibit the production of pro-inflammatory cytokine and thus inflammation (Bonaz et al., 2016; Harris, 1950). Regarding the cholinergic anti-inflammatory pathway (CAP), it takes place through a vago-vagal reflex (i.e., the inflammatory reflex) consisting in a brainstem integrated communication between afferent and efferent vagal fibers (Pavlov et al., 2003; Tracey, 2002). More specifically, when afferent vagal fibers are activated by cytokines, the inflammatory reflex occurs in the nucleus tractus solitarius and efferent vagal fibers release acetylcholine in the inflamed area. This neurotransmitter will interact with macrophages, inhibiting pro-inflammatory cytokine production and thus inflammation. Some studies suggest that the spleen would be involve in the CAP (Rosas-Ballina et al., 2011), however, it is still controversial because even if some studies (e.g., Buijs et al., 2008) have shown innervation of the spleen by the vagal nerve, others did not show innervation (e.g., (Bratton et al., 2012).

As presented in the first Chapter (see section 2.1.), excessive sympathetic activity and chronic inflammation promote cancer development. This section presented the involvement of the vagal nerve in the regulation of the sympathetic system and inflammation through the autonomic balance, the vago-sympathetic pathway, the HPA axis and the CAP. In

conclusion, the vagal nerve can indirectly regulate cancer development via regulating sympathetic activity and inflammation.

The vagal nerve activity (VNA) can be measured using heart-rate variability (HRV). HRV is the oscillation in the interval between consecutive heartbeats as well as the oscillations between consecutive instantaneous heart rates (Task Force, 1996). In other words, HRV reflects the overall variability of the heart rate. Indeed, "*a healthy heart is not a metronome*"(Shaffer et al., 2014) and the heart rate changes accordingly to every stimuli to which we are subjected; namely stress, heat, physical activity and so on. Therefore, this variability in the heart rate reflects the ability to adapt to the environment's demands and consequently the balance between the sympathetic and the parasympathetic system involved in cardiovascular homeostasis. While the sympathetic system causes the heart rate to increase, the vagal nerve causes it to decrease.

1.3. HOW TO MEASURE HEART RATE VARIABILITY

There are several ways to measure HRV (and thus VNA, see table 1). However, according to the subject of this thesis, this section will focus on time and frequency domain indicators frequently used in the field of cancer. These indicators are obtained through different interpretations of the electrocardiogram, meaning the recording of the heart rate and cardiac activity.

Table 1: Selected HRV measures

Time domain	**SDNN (ms)**	**Standard deviation of all NN intervals**
	SDANN (ms)	Standard deviation of the averages of NN intervals in all 5min segments of the entire recording
	SDNN index (ms)	Mean of the standard deviations of all NN intervals for all 5 min segments of the entire recording.
	RMSSD (ms)	**The square root of the mean of the sum of the squares of differences between adjacent NN intervals**
	SDSD (ms)	Standard deviation of differences between adjacent NN intervals.
	NN 50 count	Number of adjacent NN intervals differing by more than 50 ms in the entire recording
	pNN50 (%)	Percentage of NN50 in the entire recording
Frequency domain	Total power (ms^2)	Total power of VLF, LF and HF band frequencies
	Peak frequencies (Hz)	VLF, LF, and HF band peak frequencies (e.g., HF peak)
	Absolute power (ms^2)	Absolute powers of VLF, LF, and HF bands (e.g., HF-HRV)
	Relative power (%)	Relative power of VLF, LF, and HF bands
	LF/HF	Ratio of absolute power of LF /absolute power of HF

Time domain methods focus on the time between heartbeats. The two most common indicators used in the literature for measuring HRV and cancer or psychological factors are the standard deviation of all normal intervals (SDNN) and the root mean square of successive differences between intervals (RMSSD). Those indicators can be used in both short (5 min) and long-term (24 h) electrocardiogram recordings. They are based on the interval between normal heartbeats (see figure 5) and reflect the variability of time between heartbeats.

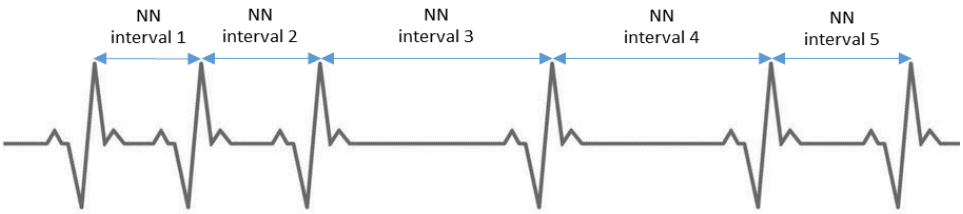

Figure 5: Time domain HRV

The frequency domain analysis is more complex and focuses on how power (variability) distributes as a function of frequency using a power spectrum density (PSD) analysis (see figure 6). In order to obtain frequency domain indicators, the physiological signal (i.e., the electrocardiogram) needs to be mathematically transformed. First, the signal is transformed from time to frequency and then those frequencies are used to create the PSD. The very low frequency (VLF) range is under 0.04Hz, the low frequency (LF) range

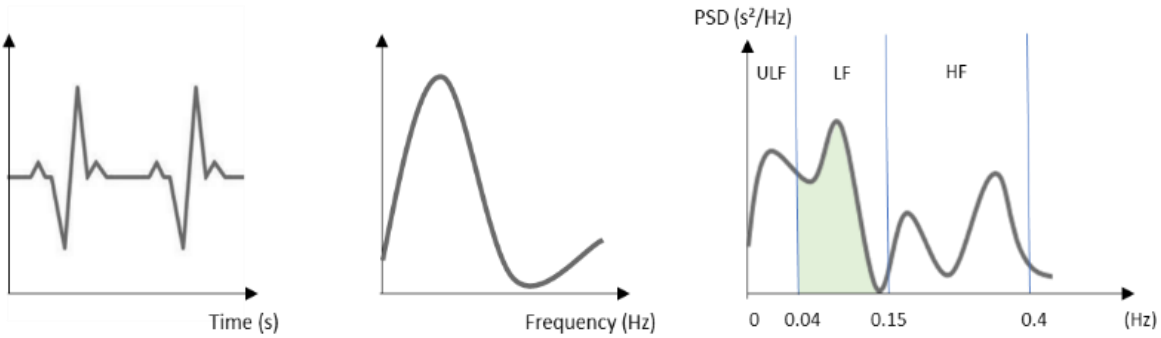

Figure 6: Transformation from time to frequency domain HRV to obtain a PSD

is from 0.04Hz to 0.15Hz and the high frequency (HF) range is from 0.15Hz to 0.4Hz. The most frequently used indicators in the literature are the absolute power of LF-HRV and HF-

HRV (e.g., (Bodin et al., 2017; Visted et al., 2017). The frequency domain focuses on how the different frequencies participate in the variability of heart beat intervals.

As both sympathetic and parasympathetic systems are involved in heart rate changes, there is a debate in the literature about which indicator reflects only VNA or the autonomic balance. However, time domain HRV is widely used as an index of VNA (e.g., De Couck et al., 2013; Gidron et al., 2018; Gross et al., 2016; Kloter et al., 2018b; Tegegne, Man, et al., 2018). The most frequent interpretation being that higher SDNN and RMSSD reflect higher variability, meaning higher vagal nerve activity, more flexibility and adaptability. Similarly, higher HF-HRV suggests higher vagal nerve activity (e.g., Giese-Davis et al., 2015; Koenig et al., 2015; Kuo et al., 2005). The LF/HF ratio is often used to evaluate the autonomic balance however, while many authors interpret LF-HRV as a sympathetic activity measure, several studies suggest that LF-HRV mostly reflects actually parasympathetic (vagal) activity, thus the interpretation of LF-HRV and its impact on the LF/HF ratio is still debated (e.g., Billman, 2013).

1.4. INCREASING VAGAL NERVE ACTIVITY: VAGAL NERVE STIMULATION

Because of the wide distribution of the vagal nerve, its involvement in regulation of biological processes related to cancer development, and due to its relationship with psychological prognostic factors, the vagal nerve is considered as a very interesting therapeutic target (e.g., Breit et al., 2018). Beside the cancer domain, HRV has gained interest for several years due to its association with physical and mental health indicators in general. Indeed, HRV is an indicator of outcomes for patients. For example HRV predicts mortality after myocardial infarction (Hayano et al., 2021) and among hemodialysis patients (Chang et al., 2020). Furthermore, HRV also predicts pain after surgery (Caton et al., 2021). In psychology, high HRV is an indicator, among others, of emotion regulation

(Visted et al., 2017; Williams et al., 2015) and is associated with psychological health and stress (Kim et al., 2018). Therefore, different techniques have been developed to stimulate the vagal nerve. In this section, two types of vagal nerve stimulation (VNS) will be presented: electrical and behavioral.

1.4.1.Electrical stimulation

Electrical VNS (eVNS) has been the first treatment targeting the vagal nerve. This method is invasive (i.e., requires surgery) as a small device is implanted under the skin and sends electrical impulses to the vagal nerve (see figure 7 below). The eVNS was first used to treat resistant epilepsy with the first reported implant in 1988 (Penry & Dean, 1990). Since then, the eVNS has been tested to treat many other diseases. For instance, the United States Food and Drug Administration (FDA) approved the eVNS treatment for resistant epilepsy, resistant depression, cluster headaches and migraines (Wang et al., 2021). For example, as a treatment for epilepsy eVNS allows a reduction of seizure frequency up to 50% at 6 month follow up (Barnes et al., 2003). In resistant depression, eVNS improves quality of life and reduces suicide (Kamel et al., 2022).

Despite those results, the main problem with the eVNS technique is its invasiveness. To overcome this limitation, two medical devices have been developed: the transcutaneous VNS (tVNS) and the auricular VNS (aVNS).

Although these devices are also based on electrical impulses to the VN, tVNS is performed through a small device on the surface of the neck and the aVNS uses electrodes on the ears. These two methods are recommenced to be used in less severe forms of disorders such as depression (Koenig et al., 2021).

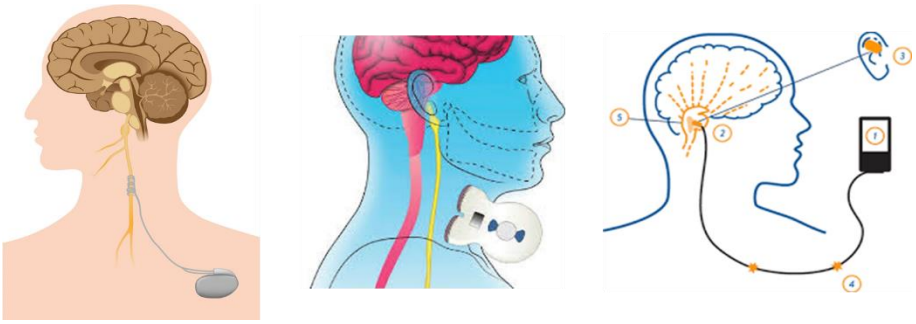

Figure 7: Vagal nerve stimulation - from left to right, eVNS, tVNS, aVNS

1.4.2.Behavioral vagal nerve stimulation

Behavioral VNS is based on either breathing exercises (bVNS) or HRV biofeedback (HRVb). Although both methods imply breath control, they differ in their instruction. On the one hand, bVNS consists of following a specific breathing pattern. On the other hand, HRVb consists of regulating one's heart rate by modifying one's breathing while receiving visual feedback on a screen about one's HR or HRV. In the field of mental health, HRV has become a target therapy in the management of psychological and psychiatric disorders: behavioral interventions using breathing are used, for example, in the management of depression (Caldwell & Steffen, 2018) or eating disorders in order to reduce food craving (Meule & Kübler, 2017).

An individual's usual breathing rate is between 12 and 20 breaths per minute (Russo et al., 2017) with a breath corresponding to an inhalation and exhalation. Many interventions use a frequency of less than 10 breaths per minute to increase HRV (e.g. 0.16 Hz, Edmonds et al., 2009; Zunhammer et al., 2013). According to Bernardi and his collaborators (Bernardi et al., 2001), HRV would be maximal when the respiration rate is 0.1Hz (6 breaths per minute). Indeed, this frequency correspond to the baroreflex

frequency. The baroreflex is a feedback system by which heart rate is modulate in response to blood pressure or breathing variation. This frequency is therefore frequently used (e.g., Hallman et al., 2011; Sakakibara et al., 2013; Tatschl & Schwerdtfeger, 2022; Van Diest et al., 2014). However, a meta-analysis of Song and Lehrer (2003) suggests that HRV would be optimal at a rate of 0.07 Hz (4 breaths per minute). Despite significant variability regarding breathing techniques, bVNS results are encouraging. Indeed, it was found to effectively modulate HRV (e.g., Laborde et al., 2022; Schmaußer et al., 2022; Vanderhasselt & Ottaviani, 2022). A meta-analysis conducted on 223 studies support the effect of to increase HRV. In addition to those results, Laborde and collaborators underline the accessibility of bVNS (low-tech and low-cost), making the voluntary slow breathing easy to implement in health-related contexts (Laborde et al., 2022).

In conclusion, the vagal nerve has multiple interesting functions as it regulates systems involved in cancer development (i.e., inflammation, excessive sympathetic activity) and psychological prognostic factors such as depression; it is possible to measure its activity using HRV, and it is possible to activate it by noninvasive methods (i.e., tVNS, aVNS, bVNS, HRVb). However, the specific relationships between vagal nerve activity and cancer onset and progression need to be addressed. This is the aim of the next section.

2. VAGAL NERVE ACTIVITY AND CANCER

Although interest in the vagal nerve is growing in the field of cancer and it had been identified as having therapeutic potential (Reijmen et al., 2018), to the best of our knowledge there is only one study which examined the effects of VNS in cancer patients (Reijmen et al., in prep). Until now, this thesis presented both cancer and vagal nerve characteristics. The purpose of this section is to present the vagal nerve in relation with cancer. Thus, the relationships between vagal nerve activity and three aspects of cancer will

be presented: first the relationship between HRV and psychological risk and prognostic factors will be examined. Second, the relationship between HRV and cancer development will be reviewed. Finally, the relationships between HRV and cancer prognosis will be developed.

2.1. HRV AND PSYCHOLOGICAL RISK AND PROGNOSTIC FACTORS

In the first chapter, the roles of psychological risk and prognostic factors in cancer such as distress and health behaviors have been detailed (see chapter 1 section 3.2). Interestingly, those factors are also associated with the vagal nerve. Indeed, lower values of HRV are found in patients who suffer from several mental health disorders such as depression (Kemp et al., 2010; Koch et al., 2019), anxiety (Cheng et al., 2022) and post-traumatic stress (Ge et al., 2020). According to some authors, HRV could even be used as an objective assessment of psychological health and stress (H. G. Kim et al., 2018). Regarding health behavior, low HRV is associated with alcohol use (Ralevski et al., 2019), smocking (Murgia et al., 2019; O'Keeffe et al., 2018) and with low physical activity (Chen et al., 2019; Estévez-González et al., 2022). Finally, a balanced diet is associated with better HRV (Young & Benton, 2018) while an unhealthy diet is associated with low HRV (Grosso et al., 2017).

Of course, the relationship between psychological and behavioral factors and the vagal nerve is actually bidirectional. In one hand, low HRV is associate with low emotion regulation (Williams et al., 2015) and HRV can be improved by emotional regulation training (Christou-Champi et al., 2015). On the other hand, as explain on the previous section, HRV stimulation can increase psychological mental health for example, in the management of depression (Caldwell & Steffen, 2018) or eating disorders in order to reduce food craving (Meule & Kübler, 2017)

These findings therefore suggest that the impact of cancer risk and prognostic factors could be limited by using interventions to increase vagal nerve activity and indirectly reduce the effect of risk factors on cancer onset and patients' prognosis.

2.2. VAGAL NERVE ACTIVITY AND CANCER DEVELOPMENT

There is some direct empirical evidence that supports the effects of the vagal nerve on cancer development and several experimental and clinical studies showed the protective effect of the vagal nerve in various cancers. Indeed, surgical or pharmaceutical removal of the vagal nerve (vagotomy) increases lungs, liver and kidney metastasis of breast cancer cells in mice. In contrast, activation of the vagal nerve via a vagal-dependent anti-inflammatory agent decreased metastasis of breast cancer tumors in rats (Erin et al., 2013). Importantly, these results have been partly confirmed in humans. Indeed, vagotomy accelerates pancreatic tumorigenesis and tumor growth through increased recruitment of tumor-associated immune cells in the tumor microenvironment and via inflammation (H. Wang et al., 2021), suggesting that the vagal nerve had an antitumor effect in pancreatic cancer. Finally, high vagal activity predicts lower levels of the tumor markers in prostate and colon cancer (De Couck et al., 2013; Mouton et al., 2012) and predicts longer survival in pancreatic cancer via reduced inflammation (De Couck et al., 2016). Moreover, in gastric cancer, lower HRV correlates with advanced tumor stage, elevate inflammation and worst outcomes, on other words with shorter survival (Hu et al., 2018).

Although a large majority of studies point to a protective role for the vagal nerve, some studies call for vigilance. An animal study suggests that vagal nerve activation may be involved in promoting cancer development (C. M. Zhao et al., 2014). This highlights the necessity to consider animal vs human models and the methodology of measuring vagal nerve activity (local vs systematic) in when interpreting the results of different studies.

Indeed, while the human study (Hu et al., 2018) has a systemic approach, the animal study conducted by Zhao et al. had a local, organ-centered approach. This suggests that the vagal nerve could have antagonist actions at different levels.

2.3. HRV AND CANCER ONSET AND PROGNOSIS

Epidemiological studies and meta-analysis have shown that high vagal activity, indexed HRV, predicted a better prognosis in various cancers, meaning a longer survival (De Couck et al., 2013; Giese-Davis et al., 2015; D. H. Kim et al., 2010; Zhou et al., 2016). The meta-analysis conducted by Zhou and collaborators even supported the independent prognostic role of HRV in cancer survival. Finally, in pancreatic cancer, the predictive role of HRV was statistically mediated by reduced inflammation – specifically lower CRP (De Couck et al., 2016), suggesting a protective role of the vagal nerve in cancer prognosis. Nevertheless, little is known about HRV and cancer onset.

In conclusion, when it comes to the vagal nerve and cancer, we know how the vagal nerve is related to risk and prognostic factors, we know that vagal nerve activity is related to cancer development and we know that vagal nerve activity even predicts cancer patients' prognosis, independent of confounders. However, little is known about vagal nerve activity and cancer onset or whether vagal nerve activation could be used in the context of cancer prevention. The last chapter of this introductory section, the rationale, will focus on those questions and their importance.

CHAPTER 3 – RESEARCH RATIONALE

1. RESEARCH RATIONALE

In the **first chapter**, we highlighted the relationship between cancer development, biological mechanisms, and psychological factors. We presented some of the most relevant biological mechanisms involved in cancer development, namely DNA mutations, cellular growth, and the involvement of the immune and the nervous systems in cancer development. We documented the effects of psychological risk and prognostic factors in certain mechanisms, such as carcinogenic effects, increased inflammation, or excessive sympathetic activity. Throughout this chapter, we have seen the importance of the neuro-immune axis in cancer development.

In the **second chapter** of this thesis, we highlighted the involvement of the vagal nerve in cancer development. First, its implication in the regulation of the neuro-immune axis. Then, we presented the numerous observed associations between the vagal nerve, psychological factors, cancer development and cancer prognosis. This chapter emphasizes the central place of vagal nerve in cancer development.

These two chapters highlighted what we know, but also what we still do not know. Indeed, risk and prognostic factors, such as life events and smoking, are associated on one hand with both cancer risk and prognosis, and on the other hand, with vagal nerve activity. Moreover, the mechanisms involved in cancer development are the same that explain the impact of risk and prognostic factors in cancer, and are also related to the vagal nerve (e.g., inflammation). While vagal nerve activity (HRV) has been recognized as an independent ***cancer prognostic*** factor in patients (De Couck et al., 2018; Zhou et al., 2016), we could wonder whether vagal nerve activity could be an indicator of risk for ***cancer onset***. Such a finding would be important for the prevention of cancer onset and for early detection.

Indeed, they are both important leverage to reduce the cancer burden worldwide. Furthermore, as explained in this theoretical section, cancer results from the interaction of several factors, which contribute to the complexity of cancer prevention. Thus, identifying an objective measure that could reflect the overall risk of developing cancer would be a major advancement in the fight against cancer.

In addition to being a potential predictor of cancer onset, we may wonder whether the vagal nerve may also moderate (increase or decrease) the effects of psychological factors on cancer development. Indeed, the effects of psychological factors on biological mechanisms are mostly explained by the activity of the autonomic nervous system. As a consequence, the vagal nerve is involved in how psychological risk factors may impact cancer development, for example via inflammation. In past studies, HRV moderated the effects of stress on biological outcomes (Weber et al., 2010) and moderated relations between brain activity and peripheral anti-tumor immunity (Ohira et al., 2013). Thus, we wondered whether the vagal nerve could be a ***moderator*** in the relationship between psychological risk factors and the risk of developing cancer. Even if there are some studies exploring the impact of life events on the breast, colorectal and lung cancer onset, to the best of our knowledge, the impact of life-threatening events on cancer onset (all cancers considered) has not been fully explored yet. Thus, we wished to test the moderating role of the vagal nerve in the relation between life-threatening events and cancer onset.

Finally, low vagal nerve activity is associated with psychological prognostic factors, and worse cancer patients' prognosis. In addition, breathing exercises can be implement in cancer care (e.g., Fournié et al., 2022; Hasuo et al., 2020) and increase HRV (Laborde et al., 2021). Thus, stimulating the vagal nerve through breathing to improve patient prognosis or reduce cancer risk, could be of huge importance. However, despite encouraging results

regarding breathing and vagal nerve activation it must be noted that there is a lack of methodological studies on which rely to develop such intervention

2. OBJECTIVES AND HYPOTHESES OF THESIS

The general aim of this thesis is to understand the role of the vagal nerve in cancer onset and to characterize its relationship with cancer risk factors. The ultimate clinical interest is to eventually introduce the vagal nerve as a therapeutic target in the prevention and management of cancer. To meet this aim, we wished to answer several questions:

1- Does vagal nerve activity predict cancer onset? (Study 1)

2- Does the vagal nerve moderate the relationship between psychological factors and the risk of developing cancer? (Study 2)

3- What is the best breathing exercise for improving vagal nerve activity? (Study 3)

To meet these objectives, we carried out three studies (see figure 8), which constitute the empirical part of this thesis. Studies 1 and 2 are retrospective longitudinal studies. The first study aimed to explore the predictive role of vagal nerve activity in cancer onset. The second study focused on the moderating role of the vagal nerve concerning the role of psychological risk factors in cancer onset. Finally, the third study was an experimental design and tested whether different breathing exercises could increase vagal nerve activity - HRV.

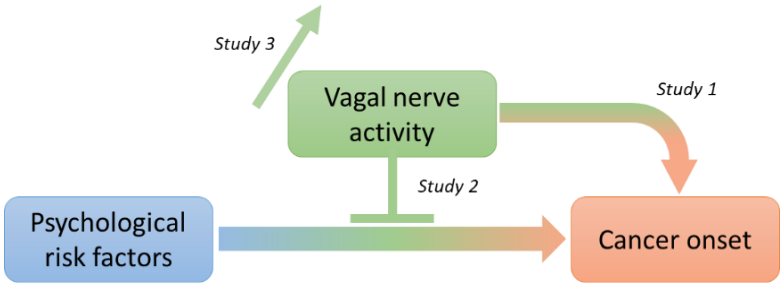

Figure 8: Representation of our three studies

3. STUDY 1

The **first objective** was to explore the predictive role of vagal nerve activity in cancer onset. In the second chapter, we underlined that the vagal nerve activity is associated with cancer prognosis; a low activity predicts a poorer survival. Furthermore, prognostic factors and risk factors are associated with vagal nerve activity and the vagal nerve inhibits crucial biological processes, which contribute to oncogenesis. Thus, we examined whether low HRV may be a risk factor of cancer onset. **Our hypothesis was that lower vagal nerve activity, measured by HRV, would predict a higher risk of cancer onset.**

To test this hypothesis, we used a longitudinal design study based on a large cohort. We thus performed a re-analysis using existing data - the Lifelines cohort (see Chapter 4). The Lifelines cohort is a longitudinal cohort, which followed over 167,000 participants over a 30-year period in The Netherlands. We included 82,768 participants (59.2% of women) who did not have cancer at baseline. Their vagal nerve activity at baseline was indexed by the HRV parameter of RMSSD obtained from brief ECGs. Cancer onset was reported during a second assessment, 5 years later.

4. STUDY 2

The **second objective** was to explore the moderating role of the vagal nerve. Indeed, in the first chapter we explained that the effects of psychological factors on biological mechanisms, which are mostly explained by the activity of the autonomic nervous system, while in the second chapter we presented the protective role of the vagal nerve. Moreover, previous studies also showed vagal activity to moderate effects of stress on the body (Weber et al., 2010) and to be a moderator between brain activity and cancer immunity (Ohira et al., 2013). Therefore, the vagal nerve may be involved in how psychological risk factors affects cancer development. Hence, we aimed to test whether the vagal nerve could be a

moderator in the relationship between psychological risk factors and cancer onset (2). **Accordingly, our hypothesis was that higher vagal nerve activity would moderate the relationship between psychological risk factors (life events) and cancer onset.**

To test this hypothesis, we used the same database: the Lifelines cohort, in order to perform a longitudinal analysis (see Chapter 5). Among other psychological variables, we decided to use the score of *Life Threatening Events* assessed at baseline. We used RMSSD as an index of vagal nerve activity at baseline and cancer onset reported during the second assessment 5 years later. We included the same sample of 82,768 participants free from cancer at baseline, as in Study 1.

5. STUDY 3

Finally, our **third objective** was to test the effects of breathing exercises on HRV. Specifically, we wished to test which pattern of breathing would be the most effective in improving vagal nerve activity - HRV. Since low vagal nerve activity is associated with adverse psychological prognostic factors, with biological etiological mechanisms in cancer, and with worse cancer prognosis, we wondered whether it is possible to increase vagal nerve activity in the most efficient manner, to reduce cancer risk and to improve prognosis (3). However, there is so far no clear evidence using strict methodology concerning which breathing pattern most effectively increases HRV. On the other hand, there is a huge variety between different breathing patterns used to improve vagal nerve activity. **Given these multiple lines of evidence, our objective was to compare, in a strict experimental design, different breathing patterns and their effect on HRV during and after the breathing exercise.**

We designed an experimental study design (see Chapter 6) to test this issue. We recruited 107 participants, who were randomly allocated to one out of 9 breathing exercise

patterns. The data of 105 participants (21 male, age range = 18–32 years old, M = 21.38, SD = 3.20 years) were analyzed. Heart rate and HRV were recorded during the whole task. Then, for each breathing exercise, we compared levels of HRV during exercise with pre-test HRV levels between the 9 breathing patterns to test the effects of the different breathing patterns on post-test HRV.

EXPERIMENTAL PART

CHAPTER 4 – STUDY 1

VAGAL NERVE ACTIVITY AND RISK OF CANCER ONSET: ANALYSIS OF THE LIFELINES COHORT

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ABSTRACT

Background: Cancer is a multifactorial fatal disease and among the major causes of morbidity and mortality worldwide. Recent studies have found that vagal nerve activity, indexed by heart rate variability (HRV), predicts longer survival in cancer. However, it is unknown whether HRV predicts cancer-onset. Since the vagus inhibits crucial biological processes which contribute to oncogenesis (e.g., inflammation), we hypothesized that high HRV may predict a reduced risk of cancer

Methods: This study used the Lifelines cohort, a longitudinal cohort study that followed over 167,000 participants over a 30-year period. Every five years, participants visited one of the Lifelines sites for a health examination. During these assessments, several physical examinations were performed (e.g. ECG, blood work) and different biomarkers were also obtained (e.g. CRP). In between assessments, participants were invited to complete follow-up questionnaires approximately once every 1.5 years. We included participants who did not have cancer at baseline. Our sample included 82,768 participants from the North of The Netherlands aged 18 and above (59.2% women). Vagal nerve activity was indexed by the HRV parameter of RMSSD obtained from brief ECGs.

Results: Our main result was that high HRV predicted a reduced risk of cancer onset, independent of several confounders (e.g., BMI, Diet, alcohol), but not independent of age. However, for people aged over 40 years old, (but not younger), high HRV did independently predict lower cancer risk.

Conclusion: This study may be the first to demonstrate that relatively higher vagal activity, indexed by HRV, predicts lower risk of developing cancer, especially among people older than age 40. These results support our hypothesis regarding the protective role of the vagal nerve in cancer and open new avenues for research on estimating cancer risk and cancer prevention.

Keywords: Vagal Nerve, Heart Rate Variability, Cancer, Lifelines

INTRODUCTION

Cancer is a multifactorial disease and is among the leading causes of mortality and global burden of diseases. Despite progress in identifying risk factors of cancer, prevention and treatment need to improve. Finding a protective factor that is inversely associated with several life-style risks factors and that inhibits biological processes which contribute to oncogenesis, may be a step forward. The vagal nerve appears to be such a candidate. The vagal nerve is the tenth cranial nerve, descending from the brainstem and innervating most visceral organs. Its activity is indirectly indexed by heart rate variability (HRV), since both correlate strongly (r = 0.88; Kuo et al., 2005). HRV reflects the fluctuations of the intervals between normal heartbeats. As smoking (O'Keeffe et al., 2018), lack of exercise (Chen et al., 2019) and unhealthy diet (Grosso et al., 2017) are well known risks factors of cancer, they are also inversely related to HRV. In fact, HRV is reduced by smoking (Bodin et al., 2017) and HRV is increased over time by physical exercise (Martinmäki & Rusko, 2008). Moreover, vagal nerve stimulation reduces obesity in animals (Ziomber et al., 2009) and

vagal nerve activation by HRV biofeedback (where people increase HRV by paced breathing) reduces food craving (Meule & Kübler, 2017). At the biological level, oxidative stress (Øvrevik et al., 2017), inflammation (Mantovani et al., 2008; Singh et al., 2019) and sympathetic hyperactivity (Magnon, 2015) all contribute to carcinogenesis. In contrast, the vagal nerve reflexively inhibits inflammation (Rosas-Ballina et al., 2011), oxidative stress (Tsutsumi et al., 2008) and of course it reduces sympathetic activity (Saku et al., 2014), being the major branch of the parasympathetic nervous system. For these reasons, the vagal nerve is hypothesized to be protective in cancer pathogenesis (Gidron et al., 2005; Reijmen et al., 2018).

Concerning predicting cancer prognosis, vagal nerve activity has a prognostic role in cancer as reviewed by a meta-analysis and a systematic review (De Couck et al., 2018; Zhou et al., 2016). Though tumor markers do not perfectly predict prognosis, HRV predicts lower levels of the tumor markers CEA in colon cancer (Mouton et al., 2012) and lower levels of PSA in prostate cancer (De Couck et al., 2013). Furthermore, high HRV predicts longer survival in breast cancer (Giese-Davis et al., 2015), lung cancer in younger patients (De Couck et al., 2013) and in pancreatic cancer (De Couck et al., 2016). The later study also found reduced inflammation to mediate the HRV-survival relationship, as expected. However, to the best of our knowledge, the role of vagal nerve activity in predicting cancer onset has not been examined. The purpose of this study was to examine the relationship between HRV and cancer onset in a large cohort study. We hypothesized that a higher HRV will predict a lower risk of cancer, independent of known risk factors. Given the relationship between certain demographic factors and HRV, such as age (Abhishekh et al., 2013), we examined the impact of these factors on the HRV-cancer onset relationship.

METHODS

This study performed an analysis of the Lifelines cohort. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167,729 persons living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics. This sample is representative of the population of the North of the Netherland (Klijs et al., 2015). Every five years, participants visited one of the Lifelines sites for a health examination. During these assessments, several physical examinations were performed and different biomarkers were also obtained. In between assessments, participants were invited to complete follow-up questionnaires approximately once every 1.5 years.

Participants

The Lifelines database includes data of more than 160,000 participants. Among these, 15,000 were children (aged 0-18), 140,000 were adults (aged 18-65) and 12,000 were elderly (65 years or older). In the present study, our cohort was composed of participants who met the following inclusion criteria: Having an ECG at baseline, being 18 years old and above. Exclusion criteria was having a diagnosis of cancer at baseline. The final cohort in the present study included 82,768 participants.

Measurements

The Lifelines database includes questionnaire data (e.g., about work, lifestyle, personality), various neurobiological measures (e.g., blood pressure, ECG, cognitive abilities) and biological samples (e.g., from blood, urine and scalp hair).

Background and patient demographics included age, gender, body mass index (BMI), alcohol consumption, total fat food consumption in kilo-calories, smoking and physical activity.

Vagal nerve activity was indexed by the HRV parameter of root mean square of successive differences (RMSSD) obtained from brief 10-sec ECGs (Tegegne et al., 2018). Such brief HRV measures predicted risk of cardiac mortality in the population (Dekker et al., 2000) and survival in patients with pancreatic cancer (De Couck et al., 2016). Furthermore, results of 10-sec HRV measures correlated satisfactorily with longer measures of HRV (Esco & Flatt, 2014).

Outcome variable

Diagnosis of cancer throughout the study period constituted our outcome variable and was assessed every 1.5 years with questionnaires and every 5 years during medical examinations. We report here diagnosis of any cancer.

STATISTICAL ANALYSIS

The primary statistical analysis was a logistic regression. Every predictor's relation with cancer-onset was tested first univariately in a logistic regression. Finally, the role of HRV in predicting cancer onset, independent of significant background predictors, was examined in a multivariate logistic regression, which considered all significant predictors of cancer onset, and HRV.

RESULTS

Sample characteristics

In total, 82,768 participants were included in this study, including 40.8% male and 59.2% female. The mean age of the sample was 43.8 ±10.8 years. Table 1 shows further details regarding the cohort's characteristics.

Does vagal activity predict cancer-onset?

In the whole sample, HRV alone significantly predicted cancer onset (Relative Risk (R.R) and 95% confidence interval (CI): R.R= 0.506, 95% CI: 0.413 - 0.620). In addition, age, alcohol consumption, physical activity score, food and fact consumption each alone significantly predicted cancer onset (see table 2).

In a multivariate logistic regression (see table 3), HRV no longer predicted cancer onset when considering the other confounders (R.R = 1.01, 95% CI: 0.81-1.26).

Since age was significantly predicted cancer onset in the present study and since HRV decreases dramatically with age in general, and since age was also negatively correlated with HRV in our sample (r=-0.38 , p<.001), we reexamined the HRV - cancer onset relationship in people below and above age 40. In this analysis, HRV was a predictor of cancer onset for people over age 40 (R.R=0.765, 95% CI: 0.607-0.963) but not in people below age 40 (R.R=0.756, 95% CI: 0.411-1.393), independent of confounders (see table 4). Hence, HRV had a significant protective relation with cancer-onset only in people older than age 40.

DISCUSSION

To the best of our knowledge, this is the first study to explore the correlation between vagal nerve activity, indexed by HRV, and future cancer diagnosis. The results of our study reveal that HRV does predict a lower cancer onset risk, but this relation depends on participant age.

HRV was a significant predictor of cancer onset in the full cohort, however, this relationship disappeared when controlling for confounders such as BMI and age. Since age significantly predicted cancer onset in the present study and since HRV decreases with age, we tested again the HRV - cancer onset relation in two age groups separately. Indeed, high HRV was a significant and independent predictor of reduced risk of cancer onset, for people over age 40, independent of confounders. In contrast, HRV did not predict cancer onset in people below age 40.

These results are in accordance with those of De Couck et al., (2013), who found that age determined when HRV predicted survival in patients with lung cancer: HRV predicted survival in younger but not older patients with lung cancer. These results also support those of (Dekker et al., 2000) who found that HRV predicts less cancer mortality in the population and those of a meta-analysis (Zhou et al., 2016) and of two systematic reviews (De Couck et al., 2018; Kloter et al., 2018) who found that high HRV predicts longer survival in patients with cancer. However, the results of the present study extend past studies to imply that HRV may be a surrogate biomarker and predictor of the onset of new cancer.

In the present study, among people over age 40, the prevalence of cancer was higher than for younger people as would be expected. In addition, HRV decreases with age (Abhishekh et al., 2013). Another important change occurring with age is increased inflammation, which contributes to all phases of cancer – escape from apoptosis,

angiogenesis and metastasis (Greten & Grivennikov, 2019a; Mantovani et al., 2008; Voronov et al., 2003). All these factors could explain why HRV predicted cancer-onset only in patients older than age 40. Furthermore, the vagal nerve inhibits inflammation by two important pathways. First, by activating the hypothalamic pituitary adrenal axis, resulting in cortisol suppressing inflammation. Second, by a descending vagal-sympathetic innervation to the spleen, where certain T cells that secrete acetylcholine, inhibit macrophages from producing inflammatory cytokines (Rosas-Ballina et al., 2011; Tracey, 2009). Indeed, one study found that reduced inflammation statistically mediated the relationship between HRV and survival in pancreatic cancer (De Couck et al., 2016). Since such an association between HRV, inflammation and cancer-onset was not observe in the present study, future studies should examine whether reduced inflammation may explain or statistically mediate the relationship between high HRV and reduced cancer-onset observed in the present study.

These results have implications for public health. For example, adults over age 40 could be periodically invited to clinics for HRV screening, to evaluate their risk and possibly prevent cancer onset and onset of other chronic diseases predicted by low HRV. Such patients could then undergo deeper genetic testing and evaluation of their lifestyle, for estimating their more precise cancer risk, because low HRV predicts many diseases. In addition, they could be encouraged to stop smoking, have a Mediterranean diet, perform moderate physical activity and do meditation, all which increase HRV (Gidron, De Couck, et al., 2018).

The limitations of this study include a short ECG for determining HRV and self-report cancer onset and not a direct link to electronic medical records, and such reported diagnosis may be subjected to recall biases. Our outcome was reported diagnosis of cancer rather than actual cancer development measured objectively in routine follow-ups.

Moreover, we could not have detailed data regarding cancer type or other parameters that are known cancer risk factors. Despite these limitations, the present study has several strengths, including a very large representative sample size, consideration of several confounders and being the first study examining whether HRV predicts reporting of cancer onset. Ultimately, the protective and causal role of the vagus in cancer should be tested by examining the effects of vagal nerve activation on cancer-onset, with a randomized controlled trial in cancer-free adults, who have low HRV and other cancer risk factors (e.g. smocking, obesity, family cancer history, carriers of BRCA). Future studies should confirm this first observation with more rigorous methodologies and plan preventative intervention trials.

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Table 1: Sample characteristics

Categorical data				Continuous data		
Variable		**N**	**%**	**Variable**	**Mean**	**SD**
Gender				Age (years)	43.80	10.80
	Male	33,785	40.8	BMI (Kg/m^2)	25.85	4.22
	Female	48,983	59.2	RMSSD (msec)	37.15	30.46
Developed Cancer				Sum of kCal	1,863.45	866.40
	Yes	1,011	1.2	Alcohol	89.51	49.84
	No	81,757	98.8	Activity Score	7,660.23	4,473.52
Smoking						
	Yes	16,431	19.9			
	No	65,605	79.3			
	NA	732	0.9			

Note: BMI = body mass index; RMSSD = route mean square of successive differences; kCal = kilocalories.

Table 2: Univariate analysis of relations between each predictor and cancer-onset

Variable	B	S.E.	Wald	Sig.	R.R	95% CI	
						Lower	Upper
Age	.058	.003	312.43	.000***	1.059	1.053	1.066
BMI	.015	.007	4.19	.041*	1.015	1.001	1.029
Alcohol	-.002	.001	11.67	.001***	.998	.996	.999
Smoking	.061	.081	.569	.451	1.063	.907	1.246
Activity score	.000	.000	34.30	.000***	1.000	1.000	1.000
Sum of Kcal	.000	.000	11.78	.001***	1.000	1.000	1.000
Fat	-.003	.001	9.042	.003**	.997	.996	.999
LogRMMSD	-.681	.104	43.30	.000***	.506	.413	.620

Note: BMI = body mass index; RMSSD = route mean square of successive differences; kCal = kilocalories**;** 95% CI = 95% confidence interval; * $p < .05$; ** $p < .01$; *** $p < .001$.

Table 3: Multivariate logistic regression of all significant predictors in relation to cancer-onset

						95% CI	
Variable	B	S.E.	Wald	Sig.	R.R	Lower	Upper
Age	.058	.003	278.348	.000***	1.060	1.052	1.067
BMI	-.006	.008	.575	.448	.994	.979	1.009
Fat	-.002	.001	2.650	.104	.998	.995	1.000
Alcohol	-.001	.001	.600	.439	.999	.997	1.001
Log-RMSSD	-.001	.113	.000	.994	.999	.801	1.246
Constant	-6.740	.345	382.684	.000	.001		

Note: BMI = body mass index; RMSSD = route mean square of successive differences; 95% CI = 95% confidence interval; *** $p < .001$.

Table 4: Multivariate logistic regression of all significant predictors in relation to cancer-onset by age

							95% CI	
Age	Variable	B	S.E.	Wald	Sig.	R.R	Lower	Upper
< 40	BMI	.019	.021	.837	.360	1.019	.979	1.061
	Fat	-.001	.004	.038	.845	.999	.992	1.006
	Alcohol	-.002	.003	.701	.403	.998	.992	1.003
	LogRMSSD	-.279	.311	.803	.370	.756	.411	1.393
	Constant	-5.165	.776	44.285	.000	.006		
> 40	BMI	-.005	.008	.437	.509	.995	.979	1.011
	Fat	-.002	.001	2.861	.091	.998	.995	1.000
	Alcohol	.000	.001	.073	.787	1.000	.998	1.002
	LogRMSSD	-.268	.118	5.180	**.023***	**.765**	**.607**	**.963**
	Constant	-3.425	.294	135.356	.000	.033		

Note: BMI = body mass index; RMSSD = route mean square of successive differences; 95% CI = 95% confidence interval; * $p < .05$

CHAPTER 5 – STUDY 2

VAGAL NERVE ACTIVITY WEAKENS THE RELATIONSHIP BETWEEN LIFE EVENTS AND CANCER ONSET: NOW THINGS ARE LESS VAGUE

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ABSTRACT

Background: Past studies found little evidence that stressful experiences predict risk of cancer. This relationship could be partly influenced by a 3rd variable. The present study examined whether vagal nerve activity, indexed by heart-rate variability (HRV) moderated the relationship between life threatening events (LTE) and risk of developing cancer.

Methods: This study performed a reanalysis of the longitudinal Lifelines Dutch cohort study. Of the initial 167,000 participants, 82,768 were included as they did not have cancer at study-entry, were at least 18 years old and had an ECG. HRV was derived from their ECG. Cancer-onset was examined over 1.5 years and several confounders were considered (e.g., age, BMI). We examined the moderating role of HRV by testing the relationship between LTE and cancer-onset separately in participants with low versus high HRV.

Outcomes: 1011 participants (1.2%) developed cancer during follow-up. LTE significantly predicted cancer-onset (RR = 1.082; 95% CI: 1.035 - 1.132). Finally, only among participants with low HRV, LTE significantly and independently predicted cancer-

onset (R.R = 1.056; 95%CI: 1.007 - 1.108), but not in people with higher HRV (R.R = 1.014; 95%CI: 0.916 - 1.122).

Interpretation: In the present study, more LTE independently predicted a higher risk of cancer development, only in people with relatively low vagal nerve activity. High vagal activity moderates the cancer-promoting effects of severe life events.

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INTRODUCTION

For over five decades, clinicians and patients have speculated whether life events and psychological factors may put people at risk for developing cancer (Ginsberg et al., 1996). Older studies used case-control studies and found that patients with cancer reported more life events than controls. Furthermore, some studies even incorrectly concluded that life events were etiological to cancer, using a case-control design (Chen et al., 1995). Strikingly, even recent studies used such methodology and found a higher risk of reporting major life events during the past 5 years in patients with lung cancer than in matched controls (Jafri et al., 2019). However, such retrospective studies suffer from recall bias and the "need to find a reason". Indeed, cancer patients often attribute their cancer to psychological sources (Dumalaon-Canaria et al., 2014). Importantly, any case-control design does not enable to infer that a variable is etiological to a disease because changes in that variable may result from having the disease, not only the opposite.

A methodologically better approach is to use longitudinal studies, where life events or psychological factors are assessed at time 1, and cancer onset is then examined at time 2. One study examined the relationship between depression and cancer risk over 24 years in 3177 people, independent of various confounders (e.g., age, gender, smoking, marital

status). They found that depression significantly predicted a nearly double risk of all cancers and over a 4 time higher risk of breast cancer, but not of other cancer types (A. L. Gross et al., 2010). In contrast, Jokela et al. (2014) examined whether personality dimensions, using the Big-Five model, predicts cancer risk, in 42,843 people, adjusting for age, gender and ethnicity. No personality dimension predicted cancer risk. Even more striking, a German study found that increased time urgency (derived from the Type-A behavior pattern) predicted a reduced risk of any cancer (Stürmer et al., 2006). In their review of over 142 studies in initially cancer-free individuals, the relationship between psychological factors and risk of cancer was significant but weak (relative risk (RR) of 1.06, and a 95% confidence interval (CI) of 1.02-1.11; Chida et al., 2008). Most of this relation stemmed from studies on depression and future risk of lung cancer.

Thus, either the relationship between stressors or other psychological factors and cancer onset is non-existent or weak. Alternatively, the inconsistent results in past studies may be due to the possibility that the stress-cancer risk relationship may be changed or modified by another factor – an effect-determinator or "moderator". One such possible moderating factor could be vagal nerve activity, whose activity is indexed by heart-rate variability (HRV; Kuo et al., 2005).

HRV reflects the changes in the intervals between normal heartbeats. The vagal nerve was proposed to have a protective role in cancer because it reduces inflammation, oxidative stress and sympathetic activity (De Couck et al., 2018; Gidron et al., 2005), factors which otherwise are pivotal in carcinogenesis (e.g., Greten & Grivennikov, 2019). High vagal activity determines faster physiological recovery in multiple body systems from stress, including inflammation (Weber et al., 2010). Furthermore, high vagal activity determines the strength of associations between brain activity and peripheral anti-cancer immunity (Ohira et al., 2013). In patients with an existing cancer, higher HRV strongly weakened the

relationship between tumor stage and future tumor marker levels (Gidron, De Couck, et al., 2018). Thus, it is also possible that high vagal may also moderate and hence weaken any relationship between major life events and future risk of cancer. This study examined the relationship between major life events and cancer onset, in a large Dutch cohort study, and examined whether vagal activity (HRV) moderated this relationship.

METHODS

This study used the Lifelines cohort, a longitudinal cohort study which followed over 167, 000 participants from the North of The Netherlands over a 30-year period. The methodology here closely resembles the method reported elsewhere on the general role of HRV in cancer onset (Caton et al. in prep). This sample is representative of the population from the North of The Netherland (Klijs et al., 2015). Every five years, participants visited one of the Lifelines sites for a medical examination. During these assessments, several physical measurements were taken and different biomarkers were also obtained. In between assessments, participants were invited to complete follow-up questionnaires approximately once every 1.5 years.

Participants

In the present study, the inclusion criteria were: having an ECG at baseline and being 18 years old and above. The exclusion criterion was having cancer at baseline. Figure 1 describes the flowchart of the inclusion of participants in the present study. The final sample included 82,768 participants.

Measurements

Background information: This included age, gender, body mass index (BMI), alcohol consumption, fat consumption, smoking and physical activity.

Vagal nerve activity was indexed by the HRV parameter of Root mean Square of Successive Differences (RMSSD) obtained from brief 10-sec ECGs (Tegegne et al., 2018). Such brief HRV measures predicted risk of cardiac and cancer mortality in the population (Dekker et al., 2000) and survival in cancer (De Couck et al., 2016). Furthermore, 10-sec HRV measure correlate satisfactorily with longer measure of HRV (Esco & Flatt, 2014).

Life Events: Threatening life events were assessed by the List of Threatening Experiences (LTE) questionnaire (Brugha & Cragg, 1990). It includes 12 experiences, asking people whether they experienced each one during the past 12 months (e.g., death of a relative, personal injury, losing one's job). The LTE correlates positively with depression and psychological distress (Rosmalen et al., 2012).

Outcome

Development of cancer was assessed every 1.5 years with questionnaires and every 5 years during medical examinations. In the present study, we report development of any cancer.

STATISTICAL ANALYSIS

The primary statistical analysis was a multivariate linear regression. Every predictor's relation with cancer was tested in a univariate logistic regression. Finally, the role of HRV in predicting cancer onset, independent of significant background predictors was examined in a multivariate logistic regression.

RESULTS

Table 1 depicts the basic characteristics of the present study's sample. Of the full sample of 82,768 Dutch residents, 1011 developed cancer during follow-up (1.5 year later), which represents 1.2 % of the full sample.

The distribution of reporting life events was as following: 0 events were reported by 41%, 1 event by 27.5%, 2 events by 17.2%, 3 events by 8.4% and more than 3 events by 5.8% of the participants. For that reason, we categorized this variable into no LTE versus one or more in the multivariate analysis below. Importantly, participants who later developed cancer initially had significantly higher mean LTE (1.27) than participants who later did not develop cancer (1.15) ($t(1057.482) = 2.446$, $p = 0.015$).

We found a significant negative, albeit small, correlation between LTE and HRV ($r = -.032$, $p < 0.001$). Additionally, and considering LTE as a categorical variable, we found that LTE significantly predicted cancer-onset (RR = 1.082; 95% CI: 1.035 - 1.132) as did HRV (R.R = 0.506; 95%CI: 0.413 - 0.620).

Among all the confounding factors, only BMI (RR= 1.015, 95% CI: 1.001-1.029), fat consumption (RR= 0.997, 95% CI: 0.996 - 0.999), alcohol consumption (RR=0.998, 95% CI: 0.996 - 0.999) and age (RR= 1.059, 95% CI: 1.053 - 1.066) were significant predictors of cancer onset. These confounders were then statistically controlled for in the subsequent multivariate analyses.

In order to explore the relation between LTE and cancer onset as function of participants' baseline HRV, we split the sample into participants with relatively low HRV versus those with relatively high HRV, and adjusted the above background variables. Only among participants with low HRV, did LTE significantly predict cancer-onset (R.R = 1.056; 95%CI: 1.007 - 1.108). However, LTE did not significantly predict cancer-onset in people with higher HRV (R.R = 1.014; 95%CI: 0.916 - 1.122). This pattern of results is shown in Table 2.

DISCUSSION

This study examined two research questions. First, whether major LTE predict cancer-onset, and second, whether this relationship is moderated by people's resting vagal nerve activity, indexed by HRV. First major LE did significantly predict cancer-onset, independent of confounders. Second, this relationship was moderated by vagal nerve activity. Specifically, we found that only in people with low HRV, did major LTE significantly predict cancer-onset, while major LTE did not predict cancer onset in those with high HRV. These results support those of (Gross et al., 2016) and of the meta-analysis of Chida et al. (2008). However, our results extend these studies' results to a Dutch sample, using a very large sample of over 80,000 adults.

Importantly, our results show for the first time that the LE-cancer onset relation is affected by people's vagal nerve activity. It is possible that the LE-cancer risk is higher in those with lower HRV because in such people, there may be less vagal regulation of inflammation (Rosas-Ballina et al., 2011) and of oxidative stress (Tsutsumi et al., 2008). Both inflammation and oxidative stress play major contributing roles in cancer development (Greten & Grivennikov, 2019; Valko et al., 2004).

Furthermore, at the psychobiological level, people with high HRV recover faster from acute stress also in their inflammatory response (Weber et al., 2010). People with high HRV may be at lower cancer risk even if having experienced severe life events since they recover faster biologically from mental stress. Finally, in people with high HRV, there is better synchronization between brain activity and peripheral anti-tumor cells (Ohira et al., 2013). For all these reasons, it is possible that people with lower HRV were at greater risk for developing cancer after exposure to major LE.

This study's results have implications for public health. First, people exposed to major LE together with lower HRV may be at higher risk for future cancer development. Since it is easy to measure HRV with current finger photoplethysmographs (e.g., Flatt & Esco, 2013), such screening could be widely implemented. Lower HRV is a risk factor of multiple fatal chronic diseases including ischemic heart disease and strokes (Gidron, De Couck, et al., 2018). Finally, future studies need to examine whether increasing vagal nerve activity by HRV biofeedback or non-invasive electrical vagal nerve stimulation may prevent the risk of cancer among people exposed to major LE with low HRV.

This study included a few limitations. First, diagnosis of cancer was based on self-report of whether patients were given a cancer diagnosis in the past year. Though the chance of reporting such a life-threatening diagnosis incorrectly is very unlikely, this was not confirmed by any lab or scanning diagnostic tests. Second, the measure of vagal activity, HRV, was derived from a very brief 10-sec ECG. This does not enable to derive the frequency-domain parameters of HRV. In addition, since it was retroactive, we do not know the precise conditions of obtaining the ECG. Nevertheless, past studies have shown that such brief measures of HRV predict death in the population (Study et al., 1997) as well as cancer prognosis and tumor marker levels (De Couck et al., 2013; Mouton et al., 2012) and survival in pancreatic cancer (De Couck et al., 2016). Despite these limitations, the present study used a large representative sample, with demographic, life-style, psychological and neurophysiological predictors of cancer-onset. The results of the present study have important implications for public health and cancer prevention.

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Table 1: Descriptive statistics of participants

Categorical data				**Continuous data**		
Variable		**N**	**%**	**Variable**	**Mean**	**SD**
Gender				Age (years)	43.80	10.80
	Male	33,785	40.8	BMI (Kg/m^2)	25.85	4.22
	Female	48,983	59.2	RMSSD (msec)	37.15	30.46
Developed Cancer				Sum of kCal	1,863.45	866.40
	Yes	1,011	1.2	Alcohol	89.51	49.84
	No	81,757	98.8	Activity Score	7,660.23	4,473.52
Smoking						
	Yes	16,431	19.9			
	No	65,605	79.3			
	NA	732	0.9			

Note: BMI = body mass index; RMSSD = route mean square of successive differences; kCal = kilocalories.

Table 2: HRV moderates the life-events-cancer onset relationship.

HRV		B	S.E.	Wald	Sig.	RR	95% C.I.for EXP(B)	
							Lower	Upper
Low	Fat	-.002	.001	2.501	.114	.998	.995	1.001
	BMI	-.009	.009	.940	.332	.991	.974	1.009
	Age	.054	.004	191.970	.000	1.056	1.048	1.064
	Alcohol	.000	.001	.012	.911	1.000	.998	1.002
	Life events	**.055**	**.024**	**4.966**	**.026***	**1.056**	**1.007**	**1.108**
	Constant	-6.594	.302	476.052	.000	.001		
High	Fat	-.001	.003	.165	.684	.999	.993	1.004
	BMI	-.004	.017	.052	.820	.996	.963	1.030
	Age	.065	.007	92.506	.000	1.068	1.054	1.082
	Alcohol	-.003	.002	2.079	.149	.997	.992	1.001
	Life events	**.014**	**.052**	**.072**	**.789**	**1.014**	**.916**	**1.122**
	Constant	-7.041	.523	181.561	.000	.001		

Note: HRV =Heart Rate Variability; BMI = body mass index; RMSSD = route mean square of successive differences; * $p < .05$

CHAPTER 6 – STUDY 3

IMPACT OF BREATHING EXERCISES ON HRV: EFFECT OF FREQUENCY AND PATTERN

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ABSTRACT

Heart rate variability (HRV) has gained interest for several years in medical and psychological studies, as elevated HRV has been associated with better health outcomes. Research has also examined whether it was possible to increase HRV based on breathing exercises. However, most of these studies show contradictory results partly due to large methodological variabilities regarding the frequency (e.g. 0.1 vs 0.07 Hz), the pattern (e.g., inhalation/exhalation ratio), the duration of exercises and the design of studies. Therefore, our study aimed to compare the effects of different breathing exercises on HRV by manipulating frequency and pattern in a between subjects design. The study included 107 participants who were randomly assigned to one out of 9 breathing exercises based on 3 frequencies (0.1, 0.08 and 0.07Hz) and 3 breathing patterns (ratio, with or without a pause between inhalation and exhalation). The task lasted 15 min during which participants had to breathe normally for 5 min (pre-test), perform one breathing exercise during 5 min, and then breathe normally again for 5 min (post-test). Heart rate and breathing rate were recorded during the whole task. Individual differences in terms of emotion regulation and coping abilities were measured by self-reported questionnaires. The main results indicate that frequency interacted with phase (baseline vs test) for LF-HRV such that 0.08Hz (and to a lesser extend 0.07Hz) was associated with a greater increased of LF-HRV compared

to 0.1Hz during breathing exercises. Results also showed that LF-HRV was higher during post-test compared to baseline, independently of frequency. Finally, we found no effect of pattern or individual differences. In conclusion, the most effective slow-paced breathing exercises to increase HRV are based on 5 breaths per minute. In addition, slow-paced breathing exercises have short-term benefit during the post-test rest period, supporting the possibility to use this technique as a relevant intervention.

Keywords: Heart Rate Variability, Breathing exercise, Slow-paced breathing, behavioral intervention

INTRODUCTION

Heart rate variability (HRV) reflects the variation existing between successive normal heartbeats and has been suggested to indicate the activity of the vagal nerve. It has gained interest for several years in medical and psychological studies as elevated HRV have been associated with multiple types of better outcomes. In medicine, high HRV is a predictive marker of survival in cancer patients (Zhou et al., 2016) and better prognosis after heart-attacks (Buccelletti et al., 2009). In the field of psychology, HRV is an indicator of the regulation of emotions (Williams et al., 2015) and of better decision making especially during risk and uncertain situations (Forte et al., 2022). As a result, HRV has become a therapeutic target in the field of physical and mental health, especially based on breathing exercises. For instance, some interventions including breathing exercises have been proposed to treat psychiatric disorders such as depression (Caldwell & Steffen, 2018) or eating disorders (Meule & Kübler, 2017). In behavioral medicine, increasing HRV was found to improve cardiovascular health outcomes (Burlacu et al., 2021). From a physiological point of view, voluntary control of breathing induces changes in heart rate and blood pressure through a mechanism called baroreflex. However, it is unclear how such mechanisms, and more globally breathing exercises, may improve mental and somatic

health. One hypothesis currently explored to explain these effects concerns the role of the autonomic nervous system (ANS): In respect to its role in mental health, modifying one's own breathing would modify the activity in different brain structures involved in the regulation of emotions via vagal afferent fibers, i.e. part of the ANS (Lehrer & Gevirtz, 2014). As depression and eating disorders are characterized by poor emotion regulation abilities, stimulating the regions involved in these abilities through breathing exercises (and increased HRV) might account for their beneficial effects. This hypothesis is supported by the fact that higher level of HRV is positively correlated with activation in multiple frontal cortical regions that regulate emotions (Thayer et al., 2012). Furthermore, changes in ANS could also explain the relationship between breathing exercises and physical health as the vagal nerve is involved in the regulation of sympathetic activity and inflammation (Bonaz et al., 2017), which are involved in several diseases such as cancer or cardiovascular diseases (e.g. Cole et al., 2015; Gidron et al., 2018; Haybar et al., 2019). Therefore, we might hypothesize that breathing exercises have beneficial effect on mental and physical health through their influence on the ANS and more specifically the vagal nerve, whose the main indicator is the HRV.

When looking directly at the effect of breathing exercises on HRV, some authors argue that 0.1Hz is the best frequency to increase HRV (e.g., Bernardi et al., 2001) while others found that 0.09Hz exercises (I. M. Lin et al., 2014) or even 0.07Hz exercises (e.g., Song & Lehrer, 2003) are more likely to improve HRV . One explanation might refer to the great heterogeneity in terms of experimental settings.

First, there are different techniques of paced breathing (breathing at an imposed rhythm with the use of visual or audio clue) which can either rely on deep breathing (deep breaths), slow breathing (breathing at a slower rate than usual), or HRV biofeedback (real-time visualization of the HRV). These techniques can even be combined with each other,

for example to perform slow-paced breathing. Moreover, these techniques have characteristics that are more or less defined by the authors in terms of duration, frequencies, pattern of breathing or use of biofeedback. Second, the duration of the exercises is also very variable from one study to another. Indeed, it can vary from 1 minute (e.g. Six Dijkstra et al., 2019) to 20 minutes (e.g. Laborde et al., 2019).

Then, if we take a deeper look in the characteristics of these exercises, we can also note an important variability in the frequency of respiration. The average breathing rate of an individual is between 12 and 20 breaths per minute (Russo et al., 2017), a breath corresponding to a inhalation / exhalation cycle. Many interventions use a frequency of less than 10 breaths per minute or 0.16 Hz (e.g. Edmonds et al., 2009; Zunhammer et al., 2013). According to Bernardi and his collaborators (Bernardi et al., 2001), HRV would be maximal when the respiration rate is 0.1Hz (6 breaths per minute). This frequency is therefore used often (e.g. Hallman et al., 2011; Sakakibara et al., 2013; Van Diest et al., 2014), even if Song and Lehrer (Song & Lehrer, 2003) suggests that HRV would be optimal at a rate of 0.07 Hz (4 breaths per minute).

In addition, for a same frequency, the breathing pattern might be different across studies in terms of the inhalation/exhalation ratio and whether or not pauses (holding breath) are incorporated either between inhalation and exhalation or between two cycles. Regarding ratios, there is a 1:1 ratio, which correspond to the same duration of inhalation and exhalation or other ratios, 1:1.5 or even 1:2. For instance, A 0.1Hz frequency might be based on exercises characterized by 5 seconds inhalation and 5 seconds exhalation (5/5) (Szulczewski & Rynkiewicz, 2018) or by 4 seconds inhalation and 6 seconds exhalation, 4/6 (Khan et al., 2013). The second ratio is based on the assumption that the use of a longer exhalation would increase the efficiency of increasing HRV and the comfort of participants. Indeed, inhalation is driven by the sympathetic system, while exhalation is driven by the

parasympathetic system, thus a longer exhalation would activate the parasympathetic system, which would increase the vagal nerve activity (Strauss-Blasche et al., 2000; Van Diest et al., 2014). In addition, it has been suggested that holding breath between inhalation and exhalation would also increase the effects of breathing exercises on HRV (Strauss-Blasche et al., 2000).

To the best of our knowledge, only few studies have tested and compared different breathing patterns on HRV. In one study with a very small sample of 5 women, results showed that the increase of HRV is greater when the breathing frequency is low (Song & Lehrer, 2003). Indeed, HRV was significantly higher at respiratory rates of 3 and 4 breaths per minute than at higher respiratory rates of 10, 12, or 14 breaths per minute However, the small sample make those conclusions difficult to generalize. Based on a protocol developed by Lehrer and collaborators (2000), another study tested the effect of several patterns among 14 participants (Edmonds et al., 2009). They indeed compared 4 patterns for a frequency of 6 breaths/minutes (0.1Hz): (a) 1:1 breathing ratio with a brief pause at the top and bottom of the breath, (b) 1:1 ratio with no pauses, (c) 1:2 breathing ratio with no pauses, and (d) 1:2 breathing ratio with a pause at the top and bottom of each breath. In a fifth exercise based on biofeedback; participants had to breathe following their heart rate in order to breathe at a resonant frequency, which is specific to each individual. The results suggest that the pattern was not relevant for breathing exercises at 0.1Hz as they all lead to an important increase of HRV. More recently, Laborde et al. (2021) tested the effects of different inhalation/exhalation ratios and the presence of pause on HRV. They showed that HRV was higher when the ratio was characterized by longer expiration than inspiration whereas pauses had no effect. However, they tested their hypothesis only with one frequency (0.1 Hz). Moreover, they used a within subjects design, thus increasing the risk of carry-over effects between different breathing patterns.

In conclusion, due to the above-mentioned methodological limitations, the previous findings should be interpreted with caution. Indeed, it remains difficult to know which breathing exercises aimed to increase HRV are the most effective. This issue had already been underlined by Zaccaro and his collaborators (Zaccaro et al., 2018) for whom it was urgent to propose a standardized methodology in breathing exercises studies.

Therefore, the present study aimed to provide a response to these limitations by comparing the impact of different frequencies and different patterns of breathing exercises on HRV. In addition, we wanted to explore the short-term effect of the exercises by testing whether their possible benefits may last several minutes after the end of the exercise. This objective result from previous findings showing beneficial short term effect after a breathing exercise at 0.1Hz (Lehrer et al., 2003).

Finally, we evaluated whether individual characteristics could be associated with the effectiveness of these exercises. Indeed, beyond the characteristics of the exercise, one can speculate about the existence of individual characteristics associated with a greater increase of HRV during breathing exercises (e.g., people with emotion regulation difficulties). Finally, the effect of baseline HRV on the effectiveness of breathing exercises was also explored.

The main objective of this study is thus to test the effect of different breathing exercises on HRV while the secondary objectives are to test individual differences in terms of emotion regulation abilities and baseline HRV.

MATERIEL AND METHODS

PARTICIPANTS

We recruited 107 participants. Due to technical problems, the data of 2 participants were not included. In total, the data of 105 participants (21 male, 84 female, age range = 18–32 years old, *M* = 21.38, *SD* = 3.20 years) were analyzed.

Inclusion criteria were to be over 18 years old, free from generalized anxiety (Module O MINI interview) and from cardiovascular diseases (self-reported). All participants gave their informed consent for inclusion before they participated to the study. The study was conducted following the Declaration of Helsinki, and the Ethics committee of Behavioral sciences of the University of Lille approved the protocol (Project identification code 2020/415/S81). Participants were recruited through an advertisement on a social network inviting them to take part in a study on breathing.

MEASURES

General information

We obtained from participants general information including age, gender, history of asthma, psychological support, smoking habits, drinking habits, physical activity practice and breathing exercises practices. Information were obtained from an ad-hoc questionnaire (i.e., *"Do you smoke?" "Do you practice breathing exercises?").*

Breathing task

General procedure

The experimental session took place in an experimental room. We installed two screens, one for the participant, used to display the instructions, and the second one for the experimenter to monitor the breathing during the exercise. We made sure that the

participants could not see the second monitoring screen. The participant also had a keyboard to start the experiment (by pressing *space*) and to answer the questions (by pressing the numeric keyboard).

Design

The experimental session was programmed with PsychoPy 3. It lasted 15 min during which participants had to breathe normally for 5 min (pre-test), perform one breathing exercise during 5 min, and then breathe normally again for 5 min (post-test).

During the pre-test (baseline), participants had to breathe as usual during 5 minutes; they had to watch neutral pictures (IAPS, Bungener et al., 2016) to reduce intrusive thoughts. These pictures (n=59) were randomly displayed on the computer screen each for a duration of 5 seconds. At the end of this phase, participants had to rate their intrusive thoughts (unwanted, unpleasant or stressful thoughts, from 0 = none to 9 = a lot) and perceived stress level (0=not stressed, to 9= very stressed) using the numeric keyboard.

For the test phase, we created nine breathing exercises based on three frequencies, 0.1Hz, 0.08Hz and 0.07Hz and three patterns (A, B and C), one without a pause and two with a pause (with two different inhalation / exhalation ratios). We obtained 9 exercises to be carried out for 5-minutes (recommended time to perform HRV analysis; Task Force, 1996). These exercises are referred to as conditions and are presented in Table 1. We excluded conditions without a break when the inspiration and exhalation were of equal duration. Indeed, these conditions would have been uncomfortable for our participants and likely to generate hyperventilation.

Table 1: Presentation of the nine breathing exercises based on frequency (0.1Hz, 0.08Hz, and 0.07Hz) and pattern (ratio and with or without holding breath)

		Pattern			
		Without holding breath		With holding breath	
		Ratio		Ratio	
		Inhale = Exhale	Inhale < Exhale (Pattern A)	Inhale = Exhale (Pattern B)	Inhale < Exhale (Pattern C)
Frequency	0.1Hz		4/6 [1]	4/2/4 [4]	3/2/5 [7]
	0.08Hz		5/7 [2]	5/2/5 [5]	4/2/6 [8]
	0.07Hz		6/8 [3]	6/2/6 [6]	5/2/7 [9]

Note : [X] = condition

Participants were randomly assigned to one breathing exercise. During this exercise, they had to follow a dot, moving up (inhalation) and down (exhalation) along a line. We monitored their breathing using BSL on another screen (that they were not able to see) to ensure they were doing the exercise correctly (i.e., visual control from the experimenter). After the exercise, participants had to assess the difficulty of the exercise (from 0= easy to 9= very difficult) and their perceived stress level (0=not stressed, to 9= very stressed) using the numeric keyboard.

Finally, the post-test was similar to the pre-test - during 5 minutes, participants had to watch the same neutral pictures randomly displayed on the computer screen for 5 seconds each and rate their intrusive thoughts and perceived stress using the numeric keyboard at the end of the presentation.

Physiological recording

Hear rate and breathing rate were recorded during the whole task and were acquired via electrocardiography (ECG) and a breathing belt, using a BIOPAC amplifier (MP35; BIOPAC Systems, Inc.) equipped with the BSL software (Biopac Systems, Inc., Santa Barbara, CA). For ECG, we placed three EL503 pre-gelled electrodes on the participants' wrists and right ankle. The breathing belt was used to monitor that the participant was

following the assigned breathing pattern instructions (Respiration Belt Transducer). The signal was digitized at a 1000 Hz sample rate. All data processing was performed off-line using the GNU Octave software package. The ECG signal was band-pass filtered at 0.5 and 35 Hz with a notch filter set at 50 Hz by the BIOPAC acquisition software. The R-R intervals were first automatically computed using custom program on the GNU Octave, and then corrected with a visual examination by the experimenter. For HRV quantification, we referred to HRV guidelines (task force) as well as the Kubios software user's guide. The R-R intervals were first detrended with a smoothness-prior method to remove the very low frequency component (below 0.04 Hz). Then, a power spectral density analysis was performed using a non-parametric method (Fast-Fourier Transform). Breathing rate was also obtain by using a custom program on the GNU Octave.

Regarding the heart rate variability indexes, we focused on RMSSD and LF-HRV before (baseline), during (test) and after (post-test) the breathing exercise. For the time domain indexes, RMSSD is a better marker of vagal nerve activity when the task requires breathing changes and provides a global measure of vagal nerve activity (Thomas et al., 2019; Pyne et al., 2019) while LF- HRV emphasizes the baroreflex and reflects the impact of breathing exercises on the cardiovascular system (Shaffer & Meehan, 2020).

Questionnaires

Cognitive Emotion Regulation Questionnaire (CERQ)

This questionnaire assesses the cognitive strategies used to regulate emotion and it is composed of 36 items. It identifies 9 strategies categorized into adaptive (acceptance, positive refocusing, refocusing on planning, positive reappraisal and putting into perspective) and less adaptive strategies (self-blame, rumination, catastrophizing and blaming other) (Garnefski & Kraaij, 2006). Participants respond on a 5-point frequency

Likert scale (almost never to almost always). The French version presents satisfactory psychometric properties (Jermann et al., 2006).

Difficulties in Emotion Regulation Scale (DERS)

This questionnaire assesses the difficulties of emotional regulation and is composed of 36 items (Côté et al., 2013; Dan-Glauser & Scherer, 2013; Gratz & Roemer, 2004). The DERS identifies 6 dimensions of emotion difficulties: non-acceptance of emotional response, difficulties in adopting goal-directed behaviors, difficulties in controlling impulsive behaviors, lack of emotional awareness, limited access to emotion regulation strategies, and lack of emotional identification or clarity. The total score indicates the overall level of emotional regulation difficulties. Participants respond on a 5-point frequency Likert scale (almost never to almost always). Regarding psychometrics, the psychometric evaluation of the French version had very good psychometric proprieties: Cronbach's alpha was 0.94, stability (test–retest) was 0.84 (Côté et al., 2013).

Brief COPE

This questionnaire assesses the different ways in which people respond to stress and it is composed of 28 items (Carver et al., 1989). The brief COPE identifies 14 coping strategies: active coping, planning, instrumental social support, emotional social support, expression of feelings, positive reappraisal, acceptance, denial, blame, religion, distraction, substances use, and behavioral disengagement (Muller & Spitz, 2003). These strategies can be grouped into 4 factors: seeking social support, problem solving, avoidance and positive thinking (Baumstarck et al., 2017). Each item is scored on a 4-point frequency Likert scale (never to very often). It was translated and validated in French and has good structural validity (Muller & Spitz, 2003).

PROCEDURE

Participants were recruited through an advertisement on a social network inviting them to take part in a study on breathing. Once they emailed us, we sent them the information letter and made an appointment for the experimental part of the study. The day before, participants received by email the link of the Limesurvey questionnaires, which took around 25 minutes to complete. To respond, participants had to create an anonymization code they had to memorize for the experimental part.

The experiment took place in an experimental room in the Laboratory and lasted approximately 30 minutes. First, participants had to fill the consent form and then we verified that they were not suffering from generalized anxiety or cardiovascular diseases. The breathing belt and electrodes were installed to measure the participant's breathing rate and heart rate throughout the study. We explained the task to the participants and gave them the instructions (e.g. trying not to move, answering with the keyboard, letting us know if they wanted to stop the experiment) before we left the room. At the end of the breathing task, we entered the room and we debriefed the participants about the purpose of the study.

Sample size calculation

Our sample should consist of 107 participants. Indeed, the statistical power calculation performed on Gpower predicts for an analysis of variances (ANOVA), 107 participants for an effect size at $d = 0.50$, a statistical threshold $\alpha = 0.05$ and a statistical power $1- \beta = 0.95$.

Statistical analysis

Statistical analyses were performed using the SPSS software package Version 28 (SPSS Inc., Chicago, IL). All analyses regarding HRV were conducted for both RMSSD and LF-HRV. Repeated measures were perform to evaluate the interaction between the 3 phases, pattern and frequency. These analyses reflect the general design of the study; however, to test our hypotheses, we will focus on repeated measures between 2 phases. Therefore repeated measures and Bonferroni post hoc analyses were used to evaluate the interaction between HRV variations between phases (within subject) and either frequency or pattern or frequency and pattern in relation to HRV, the dependent variable. The analyses of simple effects (e.g., effect of frequency on the variation between two phases) were based on mean comparisons using the relative differences (baseline vs test, baseline vs post-test, test vs post-test). Pearson correlations were used to investigate the association between these relative differences, baseline HRV, CERQ, COPE, and DERS scores. The significance level was set at $p < .05$.

RESULTS

Group characteristics at baseline

Table 2 presents the characteristics of our sample (size, age and sex) for every frequency and pattern of breathing exercises. The nine groups did not differ in terms of gender and age (*ps* >.092).

Table 2: Sample characteristics by frequency and pattern (size, mean age and SD, sex ratio)

		Pattern A			Pattern B			Pattern C			TOTAL		
		N	Mean age (SD)	Ratio male/ total	N	Mean age (SD)	Ratio male/ total	N	Mean age (SD)	Ratio male/ fe-male	N	Mean age (SD)	Ratio male/ total
Frequency	0.1Hz (1)	13	20.00 (1.87)	2/13	12	21.17 (4.02)	2/12	11	20.27 (2.19)	1/11	36	20.47 (2.81)	7/36
	0.08Hz (2)	11	22.27 (2.80)	2/11	12	21.83 (3.27)	2/12	12	22.42 (3.55)	2/12	35	22.17 (3.15)	7/35
	0.07Hz (3)	11	19.27 (1.35)	3/11	11	22.82 (3.31)	3/11	12	22.42 (4.10)	4/12	34	21.53 (3.47)	7/34
TOTAL		35	20.49 (2.38)	7/35	35	21.91 (3.52)	5/35	35	21.74 (3.46)	7/35	**105**	**21.38 (3.20)**	**21/105**

Note : Pattern A, inhalation = expiration without holding breath; Pattern B, inhalation = expiration with holding breath (2 seconds) between inhalation and exhalation; Pattern C, inhalation < exhalation with holding breath (2 seconds) between inhalation and exhalation.

Manipulation check

Based on breathing data acquired with the breathing belt of the Biopac and Kubios software analyses, we obtained participants' breathing frequency during exercise. Participants' breathing frequency fit to their allocated required frequency. For example, for participants in the 0.07 Hz group, the mean breathing frequency was 0.07 Hz with a standard deviation at 0.001Hz, thus showing small deviation from the requirement.

Baseline HR, HRV and breathing frequency

At baseline, there was no effect of frequencies, patterns or any interactions on HR, RMSSD or LF-HRV, or breathing frequency (BF) (p*s*>.08). Descriptive data (Mean and SD) for HR, RMSSD and LF are presented in Table 3.

General analyses

Descriptive data (mean and SD) of RMMSD and LF-HRV for each frequency, pattern and phase are summarized in table 4.

For RMSSD, repeated measures analyses of variance showed a main effect of phase (F(2, 192)=56.35; p<.001, eta^2=.37) and frequency (F(2, 96)=4.283; p=.017, eta^2=.082) while the effects of pattern was not significant (F(2, 96)=1.265; p=.287; eta^2=.026). Regarding interactions, none were significant (ps>.136).

For LF-HRV, repeated measures analyses of variance showed a main effect of phase (F(2, 192)=155.67; p<.001, eta^2=.62) and frequency (F(2, 96)=3.918; p=.023, eta^2=.075) while again the effect of pattern was not significant (F(2, 96)=.129; p=.879, eta^2=.003). Regarding interactions, the interaction of phase by frequency was significant (F(4, 192)=4.009; p=.004, eta^2=.077), while phase by pattern interaction was not significant (p=.996). The triple interaction of phase by frequency by pattern was significant (F(8, 192)=2.083; p=.039, eta^2=.080).

Table 3: Descriptive data (Mean and SD) HR, RMSSD, LF and breathing frequency for each frequency and pattern of breathing exercises

		Pattern A				Pattern B				Pattern C				TOTAL			
		HR	RMSSD	LF-HRV	BF	HR	RMSSD	LF-HRV	BF	HR	RMSSD	LF-HRV	BF	HR	RMSSD	LF-HRV	BF
Frequency	0.1Hz (1)	90.16 (13.32)	31.26 (9.85)	951.53 (595.70)	0.25 (0.06)	92.43 (14.58)	31.51 (23.66)	965.80 (1937.31)	0.28 (0.05)	90.84 (10.27)	25.81 (13.74)	388.34 (280.60)	0.25 (0.07)	91.13 (15.60)	29.68 (16.43)	784.20 (1180.97)	0.26 (0.06)
	0.08Hz (2)	78.26 (9.47)	35.88 (10.51)	1368.54 (1204.70)	0.25 (0.06)	83.11 (13.50)	49.36 (37.87)	782.76 (704.08)	0.25 (0.06)	82.68 (16.12)	45.74 (36.37)	1001.82 (1083.65)	0.27 (0.08)	81.44 (13.20)	43.88 (30.94)	1041.97 (1012.89)	0.26 (0.07)
	0.07Hz (3)	90.36 (10.85)	31.61 (22.54	538.66 (344.25)	0.23 (0.05)	82.18 (16.91)	51.97 (39.15)	1059.98 (1036.67)	0.25 (0.06)	91.61 (12.80)	28.62 (22.18)	972.85 (1555.04)	0.25 (0.04)	88.16 (13.96)	37.14 (29.87)	860.57 (1104.54)	0.25 (0.05)
TOTAL		86.49 (12.47)	32.82 (14.85)	952.83 (835.68)	0.25 (0.06)	86.01 (15.30)	44.06 (34.38)	932.64 (1305.48)	0.26 (0.06)	88.31 (13.61)	33.61 (26.89)	799.08 (1124.79)	0.26 (0.06)	86.93 (13.74)	36.83 (26.86)	894.85 (1097.17)	0.30 (0.05)

Note : Pattern A, inhalation = expiration without holding breath; Pattern B, inhalation = expiration with holding breath (2 seconds) between inhalation and exhalation; Pattern C, inhalation < exhalation with holding breath (2 seconds) between inhalation and exhalation; HR = heart rate; RMSSD = route mean square of successive differences, LF = low frequency, HRV = heart rate variability; BF = breathing frequency.

Table 4: Descriptive data (Mean and SD) for RMSSD and LF for each period, frequency and pattern of breathing exercises

		RMSSD			LF-HRV		
Frequency	Pattern	Baseline	Test	Post-test	Baseline	Test	Post-test
0.1Hz	**A**	31.26 (9.85)	54.55 (27.79)	34.12 (10.54)	951.53 (595.70)	6750.44 (5006.93)	1601.06 (1265.58)
	B	31.51 (23.66)	46.50 (28.77)	32.60 (22.94)	965.80 (1937.31)	5614.63 (4899.56)	796.41 (826.81)
	C	25.81 (13.74)	39.40 (15.38)	25.83 (7.72)	388.34 (280.60)	4040.10 (2764.98)	847.59 (785.34)
	Total	**29.68 (16.43)**	**47.24 (25.14)**	**31.08 (15.28)**	**784.20 (1180.97)**	**5543.68 (4424.63)**	**1102.62 (1041.68)**
0.08Hz	**A**	35.88 (10.51)	56.89 (19.68)	36.17 (12.54)	1368.54 (1204.70)	9416.03 (4596.32)	1665.96 (1292.94)
	B	49.36 (37.87)	70.74 (34.98)	43.14 (31.67)	782.76 (704.08)	6603.13 (5139.33)	1641.72 (2221.95)
	C	45.74 (36.37)	77.95 (46.87)	41.34 (26.04)	1001.82 (1083.65)	11601.09 (8959.18)	1430.84 (1177.59)
	Total	**43.88 (30.94)**	**68.86 (36.02)**	**40.34 (24.47)**	**1041.97 (1012.89)**	**9200.77 (6719.94)**	**1577.03 (1596.62)**
0.07Hz	**A**	31.60 (22.54)	51.14 (18.50)	30.12 (25.34)	538.66 (344.25)	7834.69 (4227.89)	756.96 (451.65)
	B	51.97 (39.15)	60.41 (28.13)	38.72 (16.97)	1059.98 (1036.67)	10526.17 (8145.47)	1207.92 (764.11)
	C	28.62 (22.18)	45.43 (29.33)	27.31 (16.63)	972.85 (1555.04)	6958.40 (5243.51)	1164.50 (1342.06)
	Total	**37.14 (29.87)**	**52.12 (25.88)**	**31.91 (19.96)**	**860.57 (1104.54)**	**8396.18 (6087.38)**	**1046.70 (938.52)**
TOTAL	**A**	32.82 (14.85)	54.21 (22.19)	33.51 (16.75)	952.83 (835.68)	7928.96 (4644.17)	1356.17 (1134.51)
	B	44.06 (34.38)	59.18 (31.64)	38.14 (24.48)	932.64 (1305.48)	7497.17 (6350.39)	1215.56 (1454.75)
	C	33.61 (26.89)	54.68 (36.81)	31.66 (19.42)	799.08 (1124.79)	7633.00 (6856.16)	1156.22 (1127.04)
	Total	**36.83 (26.86)**	**56.03 (30.60)**	**34.43 (20.45)**	**894.85 (1097.17)**	**7686.38 (5969.55)**	**1242.65 (1238.96)**

Note : Pattern A, inhalation = expiration without holding breath; Pattern B, inhalation = expiration with holding breath (2 seconds) between inhalation and exhalation; Pattern C, inhalation < exhalation with holding breath (2 seconds) between inhalation and exhalation; mean (SD)

Difference between Test and Baseline (RMSSD)

Repeated measures analyses of variance showed an effect of phase ($F(1, 96)=54.13$; $p<.001$, $eta^2=.36$) and an a main effect of frequency ($F(2, 96)=4.80$; $p<.01$; $eta^2=.091$). All other effects were not significant (p*s*>.27). The effect of phase showed that there was a general increase of RMSSD between baseline ($M=36.83$; $SD=26.86$) and test ($M=56.03$; $SD=30.60$; $p<.001$). The effect of frequency showed that 0.08Hz was associated with greater level of RMSSD ($M=56.09$; $SE=4.16$) compared to the other frequencies 0.1Hz ($M=38.17$; $SE=4.10$; $p<.005$) and 0.07Hz ($M=44.86$; $SD=4.22$; $p<.06$), with no differences between 0.1Hz and 0.07Hz ($p<.26$).

Difference between Test and Baseline (LF-HRV)

Repeated measures analyses of variance showed an effect of phase ($F(1, 96)=173.82$; $p<.001$, $eta^2=.64$), an interaction between phase and frequency ($F(2, 96)=4.35$; $p<.016$, $eta^2=.08$) and a main effect of frequency ($F(2, 96)=3.85$; $p<.025$; $eta^2=.074$). All other effects were not significant (p*s*>.09). The effect of phase showed that there was a general increase of LF-HRV between baseline ($M=894.85$; $SD=1097.17$) and test ($M=7686.38$; $SD=5969.55$; $p<.001$). The effect of frequency showed that 0.08Hz was associated with higher LF-HRV ($M=5128.90$; $SE=538.72$) compared to 0.1Hz ($M=3118.47$; $SE=531.97$; $p<.010$). Furthermore, LF-HRV at 0.07Hz ($M=4648.46$; $SE=546.58$) was greater than LF-HRV at 0.1Hz ($p<.05$), with no differences between 0.08 and 0.07 ($p<.53$). With respect to the interaction, whereas the effect of phase was significant for each frequency (*ps*< .001), 0.08Hz was associated with a greater increased of LF-HRV compared to 0.1Hz ($p<.026$) but not compared to 0.07Hz ($p<1.00$). Furthermore, there was a trend in favor of a greater increase of LF-HRV in the condition 0.07Hz compared to 0.1Hz ($p<.097$).

Difference between Post-Test and Baseline (RMSSD)

No effect was significant (ps >.074)

Difference between Post-Test and Baseline (LF-HRV)

We found an effect of phase ($F(1, 96)=10.07$; $p<.002$; $eta^2=.095$) with a greater level of LF-HRV during the post-test ($M=1242.65$; $SD=1238.96$) compared to the baseline ($M=894.85$; $SD=1097.17$; $p=.002$). The other effects (frequency and pattern) were not significant.

Difference between Test and Post-test (RMSSD)

Repeated measures analyses of variance showed an effect of phase ($F(1, 96)=75.16$; $p<.001$, $eta^2=.44$) and a main effect of frequency ($F(2, 96)=4.89$; $p<.009$; $eta^2=.092$). All other effects were not significant (ps>.12). The effect of phase showed that there was a general reduction of RMSSD between test ($M=56.03$; $SD=30.60$) and post-test ($M=34.43$; $SD=20.45$; $p<.001$).

The effect of frequency showed that 0.08Hz was associated with a greater decrease in RMSSD ($M=54.37$; $SE=3.71$) compared to after the other frequencies - 0.1Hz ($M=38.83$; $SE=3.66$; $p<.005$) and 0.07Hz ($M=42.19$; $SE=3.76$; $p<.023$), with no differences between them ($p<.52$).

Difference between Test and Post-test (LF-HRV)

Repeated measures analyses of variance showed an effect of phase ($F(1, 96)=144.77$; $p<.001$, $eta^2=.60$), an interaction between phase and frequency ($F(2, 96)=3.82$; $p<.025$, $eta^2=.074$) and a main effect of frequency ($F(2, 96)=4.30$; $p<.016$; $eta^2=.082$). All other effects were not significant (ps>.083).

The effect of phase showed that there was a general reduction of LF-HRV between test and post-test.

The effect of frequency showed that 0.08Hz was associated with a greater difference between post-test and test level of LF-HRV (M=5393.13; SE=527.23) compared to 0.1Hz (M=3275.04; SE=520.64; p<.005). Also, the difference level of LF-HRV at 0.07Hz (M=4741.44; SE=534.93) was greater than LF-HRV at 0.1Hz (p<.052), with no differences between 0.08 and 0.07Hz (p<.39).

With respect to the interaction, 0.08Hz was associated with a greater decrease of LF-HRV compared to 0.1Hz (p<.052) but not compared to 0.07Hz (p<1.00).

Stress and difficulty after breathing exercise

We evaluated the effect of conditions on these two self-reported variables. Regarding participants' self-reports of stress, repeated measures analyses of variance showed an effect of phase (F(1, 92)=7.619; p=.007, eta^2=.76), no main effect of condition (p=.719), and no interaction between phase and condition (p=.271). Regarding the effect of phase, the stress was lower after the exercise (M= 1.10, SD= 1.62) compared to baseline (M= 1.51, SD= 1.65; p<.001).

Regarding difficulty, univariate analyses showed an effect of frequency (F(2, 101)=3.410; p=.037, eta^2=.068), no effect of pattern (p=.203) and a significant interaction between pattern and frequency (F(4, 101)=2.836; p=.029, eta^2=.109). Effects of frequency showed that difficulty was higher for the 0.07Hz frequency (M=4.15, SD=2.22) compared to the 0.1Hz frequency (M=2.82, SD=2.04; p=.039). Difficulty at the 0.08Hz frequency (M=3.24, SD=2.46) did not differ from other frequencies (ps>.253).

Regarding the interaction, we found that condition 3 (M=6.00, SD=1.90) differed from conditions 1 (M=2.31, SD=2.21, p=.002), 7 (M=2.70, SD=1.57; p=.025) and 9 (M=3.00, SD=2.00; p=.044) while those conditions did not differ between each other and

no other differences between conditions were found (*ps*>.059). Difficulty score for each condition are reported in table 5 below.

Table 5: Descriptive data for difficulty (mean and SD) of breathing exercises by frequency, pattern and condition

		Pattern			
		A	**B**	**C**	**TOTAL**
Frequency	**0.1Hz**	2.31 (2.21) [1]	3.55 (2.16) [4]	2.70 (1.57) [7]	**2.82 (2.04)**
	0.08Hz	3.30 (2.67) [2]	3.34 (2.23) [5]	3.08 (2.71) [8]	**3.24 (2.46)**
	0.07Hz	6.00 (1.90) [3]	3.55 (1.57) [6]	3.00 (2.00) [9]	**4.15 (2.22)**
TOTAL		**3.79 (2.712)**	**3.47 (1.95)**	**2.94 (2.12)**	**3.40 (2.29)**

Note : Pattern A, inhalation = expiration without holding breath; Pattern B, inhalation = expiration with holding breath (2 seconds) between inhalation and exhalation; Pattern C, inhalation < exhalation with holding breath (2 seconds) between inhalation and exhalation. [X], condition; mean (SD).

Individual difference variables at baseline and relative differences of HRV (baseline vs test; baseline vs post-test)

- ***Baseline breathing frequency***

No correlation was found between relative differences and the breathing rate of participants at baseline (*ps*>.513).

- ***Baseline HRV***

Regarding RMSSD, for the relative difference of baseline and test, there is a negative correlation with baseline RMSSD (r= -.420; p<.001). For the relative difference of baseline and post-test we found a negative correlation with baseline RMSSD (r= -.395; p<.001).

Regarding LF-HRV, for the relative difference of baseline and test, there is a negative correlation with baseline LF-HRV (r= -.260; p=.007). For the relative difference of baseline and post-test we found no correlation with baseline LF-HRV (p=.089).

- ***CERQ***

Regarding RMSSD, no correlations were found between relative differences (baseline vs test and baseline vs post-test) and CERQ scores (*ps*>.071).

Regarding LF-HRV, the relative difference of baseline and post-test correlated negatively with the score of positive reappraisal (*r*= -.197; *p*=.044). No other correlations were found (*ps*>.065).

- ***COPE***

Regarding RMSSD, the relative difference of baseline and post-test correlated positively with the distraction score (*r*= .219; *p*=.025). No other correlations were found (*ps*>.119).

No correlations were found between LF-HRV relative differences and CERQ scores (*ps*>.067).

- ***DERS***

No correlations were found between HRV (RMSSD or LF-HRV) relative differences and DERS scores (*ps*>.075).

Complementary analyses

We found a negative correlation between baseline HRV and post-test intrusive thoughts for both RMSSD (*r* = -.205, *p*= .045) and for LF-HRV (*r* = -.235, *p*=.021). Correlation analyses also revealed a negative correlation between baseline LF-HRV and the total score of the DERS (*r* = -.247, *p*= .011). There was a correlation between post-test intrusive thoughts and the total score of the DERS (*r* = .296, *p*= .003).

DISCUSSION

Heart rate variability (HRV) has gained interest for several years in medical and psychological studies as elevated HRV have been associated with better physical and mental health. As a result, improving HRV through breathing exercises has become a therapeutic strategy to treat depression or cardiovascular diseases. However, even if several studies explored the effect of breathing exercises on HRV, their results differ. This could have resulted from testing different breathing patterns and frequencies as well as other methodological issues such as sample sizes and ways to measure HRV. Thus, the main objective of this study was to explore the effect of different breathing patterns and frequencies on HRV, within one study.

Regarding the effect of these breathing exercises on HRV during test compared to baseline, we found a main effect of phase: HRV (RMSS and LF-HRV) was higher during breathing exercises than at baseline. Going further, we found a main effect of frequency for LF-HRV and RMSSD, such that they were higher for 0.07Hz (LF-HRV) and 0.08 Hz (LF-HRV and RMSSD) compared to 0.1Hz. Importantly, frequency interacted with phase for LF-HRV, indicating that 0.08Hz (and to a lesser extend 0.07Hz) was associated with a greater increased of LF-HRV compared to 0.1Hz. These results thus differ from the consensus that the best frequency to increase HRV should be 0.1Hz (Bernardi et al. 2001). Indeed, it is admitted that 0.1Hz correspond to the coherent or resonant frequency at which the improvement of HRV will be the greatest. Contrary to these findings, we found that the higher HRV increase was associated with a frequency of 0.08Hz (5 breathing cycle/min), thus questioning the assumption that 0.1Hz should be the most appropriate frequency. However, other studies' results suggested that 0.1Hz is not the best frequency to improve HRV, such as Song and Lehrer (2003) or Lin and collaborator's (2014) who respectively

found that 0.07 and 0.09Hz were more effective frequency than 0.1Hz. Several reasons can be proposed to explain those differing results.

First, one can hypothesize that individuals' own resonant frequency might also account for our findings. Resonant frequency is specific to each individual and thus actually slightly differ between individuals in the range of 0.075 to 0.12 Hz (Vaschillo et al., 2006). Thus, we may wonder whether our sample had a different average resonant frequency than in the other samples. Indeed, we know for instance that resonant frequency is influenced by the height; taller people has lowest resonant frequency (Vaschillo et al. 2006). However, we did not obtain this variable to control for its effects, which would definitely be included in future studies. Moreover, mean age was higher in the study proposing 0.07Hz as the best frequency (Song & Lehrer, 2003) compared to our, which could explain differences of optimal frequency. Those results suggest that variables such as age or height may affect individuals' resonance frequency, and may account for our findings, explaining the difference of optimal breathing frequency for increasing HRV.

Second, articles showing a higher effect of 0.1Hz exercises are mostly HRV biofeedback (HRV-B) exercises (e.g., Lehrer et al., 2000). However, and similarly to the studies of Song and Lehrer (2003) and Lin et al. (2014), our study was not based on biofeedback but on slow-paced breathing with visual indication. On one hand, HRV-B is based on the voluntary control of breathing in order to maximize the respiratory sinus arrhythmia (RSA) and make it match the heart rate pattern. The biofeedback allows the participant to visualize in real time both the RSA and HR pattern, to adjust their breathing in order to make the match. The goal is to obtain the synchronization of both signals, which appears to be maximal around a frequency of 0.1Hz (Lehrer & Grevitz 2014) and associate with increase HRV. On the other hand, slow-paced breathing do not target this synchronization, as it is only base on a breathing exercise, without consideration of such

synchronization. Therefore, we could wonder whether the increase in HRV is related to synchronization of HR and breathing or whether 0.1Hz frequency is really a relevant frequency for breathing exercises that do not target a synchronization. In other words, slow-paced breathing with and without biofeedback may actually require different optimal frequencies.

Interestingly, we did not find any effect of pattern. These results replicate those of Edmonds et al. (2009) which showed that the pattern of breathing has no impact on the effectiveness of breathing exercises at 0.1Hz. However, Lin et al. (2014) found that the pattern was actually important at a frequency of 0.09Hz. However, in our study we did not test patterns involving 1:1 ratio, indeed, we believed that this ratio could have lead participants to experience discomfort and hyperventilation (e.g. Szulczewski & Rynkiewicz, 2018). Therefore, further studies should include this ratio to examine whether breathing pattern is a relevant factor affecting HRV.

Regarding the short-term effect of breathing exercises on HRV, very few studies have examined this question (e.g., Lehrer et al., 2003. In this study, we found that LF-HRV was higher after the exercise than at baseline, independently of frequency and pattern. This result is interesting as it indicates that the beneficial effect of short breathing exercise might be maintained for at least 5 minutes. Similarly, Lehrer and collaborator's (2003) also found short term beneficial effects on LF-HRV. Those short term effect suggest that training could actually have long-term effect. Indeed, patients who had cardiac rehabilitation program with HRV-B intervention had better prognosis than patients who had cardiac rehabilitation program without HRV-B (Yu et al., 2018). Moreover, they reported less depression and hostility after intervention and at 1-year follow-up. Regarding depression, HRV-B was found to improve the effectiveness of a standard treatment on depressive symptoms however; this effect did not last at 1-year follow up (Tatschl et al., 2020).

Therefore, future studies should examine long-term effect of slow-paced breathing in different patient groups and conditions.

The secondary objective of this study was to test associations between individual difference variables such as emotion regulation abilities, with baseline HR, HRV and breathing rate (BR). We found that baseline HRV (LF-HRV and RMSSD) is correlate to the relative increase of HRV. We found similar results for LF-HRV and RMSSD; suggesting that participants with lower HRV at baseline have a greater increase of HRV during exercises and better maintain of short-term effect. This result is interesting from two respects. In one hand, it highlights the importance of having comparable groups in terms of baseline HRV. However, it also suggests that it may be relevant to test the effect of several slow-paced breathing exercises on participants with low versus high HRV. Regarding BR at baseline, we found no relation with the relative increase. In respect to the role of emotional regulation differences, we found no profiles that could particularly benefit from the effects of different breathing exercises on HRV. However, even if our study do not reveal individuals' characteristic effect on the efficacy of breathing exercises, we may wonder whether other characteristics may explained our findings. For example, the resonant frequency of participants may be impacted by their height (taller got lower resonant frequency) or gender (lower frequency for men than women) (Vaschillo et al., 2006). In our sample, we do not have enough male participant to test the effect of gender on the efficacy of breathing exercises; therefore, it might be relevant to test the effect of gender on breathing exercises. Finally, Lin and collaborators' collected their sample in Taiwan, while we collected ours in France. Therefore, we can wonder whether cultural differences might explain our different results regarding the most effective frequency to increase HRV as culture is related to lifestyle factors such as diet, which affect HRV.

This study has several implications. First, one frequency (0.08 Hz) was the most effective to increase HRV during breathing exercises and was not associated with particular difficulties. However, we also show that all frequencies had a positive effect on HRV. Those results confirm that HRV is actually an interesting therapeutic target because of its prognostic role in many diseases (e.g., cancer; Zhou et al., 2016) and because it can be easily increased with different breathing patterns. It is indeed easy to improve with simple behavioral exercises, and more specifically with breathing exercises based on 4 to 6 breaths per min. Whereas the present findings suggest that 5 breaths per min (0.08Hz) should be favored (independently of pattern), the two other frequencies might also significantly increase HRV, even if it is to a lesser extent. Second, we found that the beneficial effect of slow-paced breathing exercises is maintained after the exercise, suggesting the possibility to obtain long-term effect with training or regular practice.

Finally, from a methodological point of view, our study highlights the importance of specifying all the exercises' characteristics (frequency and pattern), the relevance of using visual guidance for breathing exercises and the importance of performing a manipulation check.

Although this study addressed several limitations of previous studies, it also has some limitations. First, our sample is composed of healthy young adults. While cardiovascular diseases were exclusion criteria, 16 participants reported having asthma (but without any effect on the present results). However, one cannot rule out the possibility that diseases affecting breathing capacity could be associated with higher difficulties in following the breathing instructions and with lower effectiveness in increasing HRV. In addition, we only examined the short-term effects of breathing exercises. The long-term effect of breathing exercises on HRV is the most important clinical interest and some exercises could be more effective to increase HRV on long-term. Hence, these findings shoul be replicated with

patient samples such as cancer patients. Moreover, the present study does not allow to make conclusions about the frequency of practice (e.g., daily or weekly) that would be necessary to increase HRV on the long run. Future studies need to examine these issues. Finally, the effects described are mainly observed in relation to LF-HRV and not RMSSD, similarly to several research (e.g. Yu et al., 2018, Tatschl et al. 2020). This highlights the necessity to analyze both time and frequency domain HRV parameters.

With respect to clinical implications, the use of breathing exercises for therapeutic purposes demand frequent practice, thus requiring adherence from the patients. The present study suggests that the 5-minute breathing exercise at 0.08Hz is effective and easy to follow, which could be performed on a regular basis. However, to develop an effective intervention based on breathing exercises, several questions still have to be clarified. First, we need to replicate this study in a long-term design in medical settings, in order to confirm the hypothesis that breathing exercises could increase HRV on the long run and improve health outcomes. For instance, patients with cancer might benefit from these interventions in order to improve their prognosis. In addition, we need to test the effect of exercises duration (e.g., 30-minute), to verify if a longer exercise can be more effective than a shorter one (5-minute). Finally, we need to explore the frequency of training to verify whether one daily or weekly exercise could be sufficient to obtain a long-term increase or if it needs to be repeated several times a day. Those questions are crucial to develop the most effective but also the most acceptable intervention for patient.

In conclusion, this study revealed that slow paced breathing exercises based on 5 breaths per minute are the most effective to increase HRV, even if 4 and 6 breaths per minute are also effective but to a lesser extent. This study also revealed that these exercises have short-term benefit during the post-test rest period, supporting the possibility to use this technique as a relevant intervention for disorders characterized by low HRV. Our

results also suggest that breathing exercises frequency is the main factor to take in consideration in order to improve HRV and individuals might choose the pattern that better suits them in terms of comfort as long as they breathe at a certain frequency.

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DISCUSSION

1. MAIN FINDINGS

The general aim of this thesis is to understand the role of the vagal nerve in cancer onset and to characterize its relationship with cancer risk factors. In the first chapter of this thesis, we presented how psychological factors, related to both mental health and health behaviors, could lead to DNA mutation, inflammation or excessive sympathetic activity, which will then influence cancer development. Indeed, we explained how chronic stress (resulting from depression, anxiety, or life events) may activate the sympathetic nervous system, the hypothalamic pituitary adrenal (HPA) axis and affect the immune system and inflammation (Hong et al. 2021). We also highlighted how health behaviors influence biological mechanisms. For example, some health behaviors such as diet, smoking or alcohol consumption are associated with carcinogens (Sankpal et al. 2012). Others health behaviors may lead to inflammation, autonomic imbalance, dysregulation of the HPA axis, increased cytokines and growth factors (e.g., Han & Ham, 2021; Vucenik & Stains, 2012). Those biological mechanisms are involved in every stage of cancer development, from mutagenesis to metastasis (e.g., Hatta et al. 2021, Kamiya et al. 2019, Liu et al. 2021, Xanthopoulos et al. 2021). In other word, psychological factors and biological mechanisms influencing cancer onset and prognosis have some common pathways.

The present thesis focused on cancer onset and more specifically on the roles of the vagal nerve as another possible relevant predictor of cancer onset. As presented in the second chapter, the vagal nerve is associated with psychological risk and prognosis factor as well as cancer patient prognosis. Indeed, lower values of HRV are associated with risk and prognostic factors such as depression, anxiety, alcohol use or low physical activity (Estévez-González et al., 2022; Kemp et al., 2010; Koch et al., 2019; Ralevski et al., 2019).

Moreover, the vagal nerve is a key component of the neuro-immune axis which is involved in the regulation of the sympathetic and the immune system (both involved in cancer development). Finally, the vagal nerve activity (indexed by HRV) is proposed as a prognostic factor for cancer patients (e.g. Zhou et al. 2016).

In conclusion, we highlighted that risk and prognosis factors are similar for both onset and prognosis, that the vagal nerve is related to those factors, to the regulation of processes involved in cancer development and that its activity can be considered as a prognostic factor. Despite these common factors and mechanisms, the majority of the literature mainly focused on HRV and cancer prognosis, leaving its role in cancer onset under-examined.

Therefore, we explored the predictive role of HRV in cancer onset (**Study 1**), to answer our first hypothesis: **does vagal nerve activity (HRV) predict cancer onset?** Based on a prospective dataset, we found that HRV was indeed a predictor of cancer onset but only for people over 40 years old.

Additionally, several studies suggest a moderating role of vagal nerve activity. For instance, it moderates the association between brain activity and immune responses in acute stress situations (Ohira et al. 2013) and moderates the effects of acute stress on the body (Weber et al., 2010). Thus, we decided to conduct another study to explore the moderating role of vagal nerve activity in the relationship between psychological factors and cancer onset (**Study 2**) and answer our second hypothesis: **does vagal nerve moderate the relationship between psychological factors and cancer onset**? In this study, we tested our second hypothesis on life threatening events and cancer onset and found that vagal nerve activity is a protective factor against the effect of life-threatening events on cancer onset.

The moderating effect of the vagal nerve on such risk factor encouraged us to explore the vagal nerve as a potential therapeutic target in the prevention and management of cancer. One behavioral intervention for achieving that is breathing exercises. However, due to contradictory results concerning the effectiveness of breathing techniques, we decided to conduct an original experimental study in order to explore the effects of different breathing exercises on HRV by controlling for frequency and pattern. Thus, in a third study (**Study 3**) we explored the effectiveness of several breathing exercises in order to answer our last hypothesis: **what is the best breathing exercise to improve vagal nerve activity?** We found that the efficacy of breathing exercises depends on their breathing frequency. Indeed, while every frequency (0.1, 0.08 and 0.07 Hz) lead to a significant increase of HRV, the greater increase was found for 0.08 Hz breathing exercises for RMSSD and for both 0.08 and 0.07 Hz for LF-HRV. Moreover, we found that low HRV before the breathing exercise was associated with higher increase during the exercise. On the contrary, patterns of exercises did not affect the effectiveness of exercises.

In the following sections, we will discuss the results of these studies, meaning address their limitations and have a comprehensive discussion of our results in order to clarify them and highlight their contributions. Then, we will propose to refine the model presented at the beginning of the discussion with our results. To conclude we will develop our future directions.

2. DISCUSSION OF OUR RESULTS

2.1. VAGAL NERVE ACTIVITY AND CANCER ONSET

Our first objective was to explore the predictive role of vagal nerve activity in cancer onset. Our hypothesis was that lower vagal nerve activity, indexed by HRV, would predict a higher risk of cancer onset. To test this hypothesis, we used a prospective design study based on a large longitudinal cohort: the Lifelines cohort (see Chapter 4). This design allowed us to include 82,768 participants (59.2% women) who did not have cancer at baseline. Their vagal nerve activity at baseline was indexed by the HRV parameter of RMSSD, and cancer onset was reported during a second assessment, 5 years later. In the whole sample, HRV alone significantly predicted cancer onset (Risk Ratio=0.506). In addition, age, alcohol consumption, physical activity, food intake and fat consumption also predicted cancer onset. However, after statistically controlling for the effects of all those predictors in a multivariate analysis, HRV did not predict cancer onset anymore. Since age is an important risk factor of cancer, even the most important according to the WHO, we decided to split our sample into younger and older participants at age 40. We found out that HRV was a significant and independent predictor of cancer-onset but only for people over age 40. Our hypothesis was thus partly validated: lower HRV predicts a higher risk of cancer onset after age 40.

First, to discuss this result, we need to address statistical consideration. Indeed, we had 26682 participants under 40 for 56086 over 40 and only 0.5% whom had cancer under 40 while 1.5% had cancer over 40. Thus, we may have a lack of statistical power under 40, which may lead to observe the predictive role of the HRV only in participants over 40. Another way to interpret this result is to consider the build-up of risk. Indeed, over 40 years old, risk of cancer increase due to a build-up of risk factors such as exposure to

environmental risk factors, low physical activity or unhealthy diet (Botteri et al., 2020). While the risk of cancer increase after 40 years old, HRV decreases with age. Our results showed that HRV predict cancer onset; lower HRV is associate with a higher risk of cancer. Therefore, our results might suggest that HRV is an indicator of the overall risks in cancer onset. Thus, we can wonder whether maintaining a high HRV despite age would be a protective factor. Therefore, HRV appears to be a potential target to prevent cancer.

The relevant role of age has already been observed in the article of De Couck et al., (2013), who found that age moderated the effect of HRV on survival in patients with lung cancer. In their study, they found that HRV predicted survival only in patients under 65 years old. Seemingly contradictory, these findings might actually not be comparable with ours. Indeed, the probability to maintain high HRV above 65 years old is very low, thus preventing to test the hypothesis of the protective role of the vagal nerve. However, both studies suggest that HRV may appear to be a potential therapeutic target to prevent cancer onset and improve patient prognosis, especially in patients aged between 40 and 65.

The present study had several limitations. Indeed, it was based on a short ECG recording, self-reported cancer onset and most importantly, a retrospective longitudinal design. Regarding the short ECG, many studies have been using very short ECG recording to extract time domain indices and several showed that indices obtain from short ECG correlate highly with those obtained from longer ECG (e.g., Munoz et al. 2015, Nussinovitch et al. 2011). However, short ECG do not allow frequency analyses, which would have been more relevant in our case to measure parasympathetic activity. Indeed, LF-HRV is a better indicator of vagal nerve activation (Reyes del Paso et al. 2013). About the self-reported cancer diagnosis, it is very common to ask patients or participants about their health, their health behaviors or their antecedents. Whereas one may argue that

participants might have not reported their cancer, we believe that the probability to not report it was really low. Finally, the more relevant design would have been a longitudinal study rather than a retrospective one. The main limitation to use a retrospective longitudinal is that we do not have any control on the variables that were included. Whereas the database included some relevant factors (e.g, smoking habits), a longitudinal study would have allowed us to integrate important psychological risks factors such as depression, anxiety, hostility, or PTSD (e.g., Dyball et al. 2019, Wang et al. 2020). A longitudinal design would have also allowed us to integrate questions about health behaviors. Indeed, this would have allowed us to control their effect on cancer onset and HRV.

Besides these limitations, this study is, to the best of our knowledge, the first one to present the predictive role of vagal nerve activity in cancer onset. Therefore, the present findings represent a great step forward in cancer prevention. Indeed, HRV could be used to identify people at risk in order to prevent cancer onset or to propose early management of cancer in order to increase patients' prognosis. Regarding screening campaign, they are mostly based on age, which results in millions of costly tests. For example in France, in 2017-2018, while 5 million women over 50 years old had a mammogram, only 40,000 cancers have been detected (Santé Publique France, 2021). Thus, HRV could be used as a pre-screening tool to target more efficiently the population at risk in order to reduce the number of costly exams with this type of prevention campaign.

2.2. HRV MODERATES LTE AND CANCER ONSET RELATIONSHIP

Previous studies suggest a moderating role of vagal nerve activity on biological and clinical outcomes (Gidron et al., 2014; Ohira et al., 2013; Weber et al., 2010).Thus, we decided to explore the effect of vagal nerve activity in the relationship between psychological factors and cancer onset. Our hypothesis was that higher vagal nerve activity would moderate the relationship between life threatening events (LTE) and cancer onset. To test this hypothesis, we used the same cohort, in order to perform a retrospective longitudinal analysis (see Chapter 5). We used RMSSD as an index of vagal nerve activity at baseline and cancer onset reported during the second assessment, 5 years later and included the same sample of 82,768 participants free of cancer at baseline.

We found that LTE did not predict cancer onset but that vagal nerve activity does moderate this effect. Indeed, LTE predicted cancer onset only in people with low HRV suggesting a protective role of HRV. The non significant effect of LTE on cancer onset is in line with the meta-analysis of Chida et al. (2008) which showed that stressful life events did not predict cancer onset (even if it predicted cancer mortality). Interestingly, their results might actually be accounted by the moderating effect of the vagal nerve.

In terms of underlying mechanism, one may hypothesize that HRV moderates the effect of such events on cancer onset either because of its association with emotion regulation abilities (e.g., Visted et al. 2017) or the ability of the vagal nerve to regulate the HPA axis. On the one hand, emotional regulation competences will allow patients to regulate the level of stress experienced during the LTE, which will consequently regulate the activation of the HPA axis. On the other hand, the vagal nerve may directly regulate the HPA axis. Therefore, HRV could affect the effect of LTE on cancer onset through two pathways.

Despite the contribution of the study, it also suffered from the same limitations of the first one (short ECG, self-report cancer onset and a retrospective longitudinal design). Regarding the design of the study, elaborated a longitudinal study would have allowed us to add more variables as explain for the first study. This would have allowed us to test the moderating effect of HRV between other psychological variables such as depression or anxiety and cancer onset. Another important limitation is the scoring of the LTE questionnaire. Indeed, because the score ranged from 1 to 5, it did not allow to obtain a large variability, which explains the small difference between groups (with vs. without cancer) and the small effect size. Moreover, this questionnaire do not allow to measure the appraisal of those events, which may impact their effect on psychological wellbeing and thus on health. For instance, the death of a parent will not be appraised similarly regarding the conditions in which it happened, whether it was a natural death due to aging or more an unexpected death. Therefore, more than life events, their appraisal need to be taken in consideration to understand there effect on cancer onset.

From a clinical perspective, our findings are interesting because they highlight the moderating role of the vagal nerve and thus the protective role of the vagal nerve regarding psychological risk factors. More importantly, they opens new management perspectives concerning the protective role of HRV on the effect of non-modifiable risk factors such as LTE. Indeed, one can hypothesize that HRV is an interesting leverage especially to counteract the deleterious effect of non-modifiable risk factors (e.g., past events, environmental exposure) such that increasing vagal nerve activity could be a strategy to reduce cancer risk or improve patients' prognosis in individuals at risk.

2.3. BREATHING EXERCISES AND VAGAL NERVE ACTIVITY

Our third objective was to identify the best breathing exercise to improve vagal nerve activity through slow-paced breathing exercises. Previous research had examined whether it was possible to increase HRV based on breathing exercises. Most of them show contradictory results partly due to large methodological heterogeneity regarding the frequency (e.g. 0.1 vs 0.07 Hz), the pattern (e.g., inhalation/exhalation ratio) the duration of exercises and the design of studies (e.g., between or within-subjects). Therefore, we conducted an experimental original study aimed to compare for the first time the effect of different breathing exercises on HRV by manipulating their frequency and pattern (see Chapter 6).

These present research have several implications in general population. First, it confirms that HRV is actually easy to improve with simple behavioral exercises. Regarding the effect of these exercises on HRV during exercises, we found that even if all exercises lead to a significant increase of HRV, the frequency which lead to the greater increase is 0.08Hz (5 breathing/min). Secondly, our results highlight that slo-paced breathing exercises had a short-term effect after the breathing exercises. Finally, it reveals that baseline HRV correlate to the relative increase of HRV, thus participants with lower baseline HRV had greater increase during exercises and better short-term effect. Our study suffer from limitations that have been addressed in Chapter 6, moreover, our results had been discusses in a general context in this previous chapter, thus this section will aim to discuss our results in respect of cancer.

In our initial discussion (see Chapter 6), we proposed that individual resonant frequency may be related to the effectiveness of breathing exercises. A recent study explored resonant frequency in cancer patients (Hasuo et al., 2021) and found similar

results as in general population. Indeed, similarly to Vaschillo and collaborators (2006) they found that height was the main individual characteristics associated with the resonant frequency and that there is the same variability of resonant frequency among patients. Finally, the average resonant frequency was around 6 breaths per minute (0.1Hz) in cancer patients, similarly as numerous studies in general population (e.g., Lehrer et al., 2000; Lehrer & Gevirtz, 2014). Those results suggests that breathing exercises developed in general population could be applicable to cancer patients.

Our study highlight that participants with lower HRV at baseline have a greater increase of HRV during exercises and a better maintain of short-term effect. As cancer patients have lower HRV than general population (De Couck & Gidron, 2013), we may hypothesize that breathing exercises might be even more beneficial for them. However, only few studies explored the effect of breathing exercises on cancer patients while the evidence of linking HRV (and more largely, the vagal nerve) to cancer are growing as presented in the Chapter 2. A feasibility study had been conducted with hematologic cancer patients (Fournié et al. 2022). The 12 weeks HRV-B protocol consisted of 10 supervised 1h session and daily home practice during 20 min. They assessed the adhesion of the 20 patients included. Interestingly, only one patient dropped out due to time constraints. They had a 98% participation rate to the supervised HRV-B sessions at the hospital and an average of 6 sessions/week done while they were instructed to have a daily practice at home. No adverse event was reported. HRV-B combined to physical exercises lead to an increase LF- HRV.

A randomized study on patients with incurable cancer tested the effect of HRV-B on sleep disturbance (Hasuo et al. 2020). Patients of the intervention group had 2 hospital-based HRV-BF session (at the beginning and the end of the intervention), followed by daily

home-based HRV-B sessions (between 5 and 30 minutes) while the control group only had the hospital-based session of HRV-B. The study also report good completion rates of 96% in the intervention group and 92.0% in the control group. Daily home-based HRV-B sessions improved both sleep function and HRV within 2 weeks after intervention. Moreover, they both reported good adhesion of cancer patients to daily home based HRV-B. Finally, a pilot-matched controlled study with patients suffering from metastatic colon cancer tested the effect of daily 20 min HRV-B in addition to usual treatment during 3 months. This study, conducted on 6 patients (3 patients in the control group, and 3 in the HRV-B group), report an important reduction of tumor marker in the HRV-B group compared to patients who only received usual treatment. Despites the limitations of those studies, their results confirm the feasibility and the acceptability of such intervention. Moreover, they confirm that breathing exercises are relevant for cancer patients as they shown an improvement of HRV, psychological and physical symptoms (reducing of sleep disturbance and improvement of physical capacity).

Regarding the breathing exercise, our study was not based on HRV biofeedback but on slow-paced breathing (SPB). While HRV-B purpose is to obtain the synchronization of RSA and HR, SPB purpose is to slow the breathing rate. However, both exercises lead to an increased HRV. While SPB can be done without support, or with a simple application on smartphone (e.g., Laborde et al. 2019), HRV-B requires more material. Indeed, it requires to monitor and display HR and even if portable devices are now available and used (e.g., Hasuo et al. 2020), it is an important cost for the patient or the hospital. Thus, we could wonder whether SPB would not be more adapted for patients, future studies need to test the effect of SPB and whether they are similar to HRV-B in cancer patients.

Finally, in respect to clinical perspective, the use of breathing exercises for therapeutic purposes might imply frequent practice, thus requiring compliance and adherence from the patients. The present study show that the 5-minute breathing exercise at 0.08Hz is effective and easy to follow, which suggest that it could be performed on a daily basis. However, to develop an effective intervention based on SPB, several questions still have to be clarified. First, we need to replicate this study in a long-term design in medical settings, in order to confirm the hypothesis that breathing exercises could increase HRV on the long run and improve health outcomes. For instance, patients with cancer might benefit from these interventions in order to improve their prognosis but also their quality of life. Then, we need to test the effect of exercises duration (e.g., 5 vs. 30 minutes), to verify if a longer exercise can be more effective than a shorter one. Finally, we need to explore the frequency of training to verify whether daily, every other day or weekly exercise could be sufficient to obtain a long-term increase. Those questions are crucial to develop the most effective but also the most acceptable intervention for patients.

3. REFINING THE MODEL

At the beginning of this thesis, we used a basic linear model to illustrate the relationship between psychological factors, biological mechanisms and cancer development. (figure 1 below). However, this model was unable to explain why similar psychological factors do not have the same impact for all sample participants, and this is revealed by the weak effect-size found in meta-analyses on the prognostic role of certain psychological factors in cancer (e.g., Chida et al., 2008).

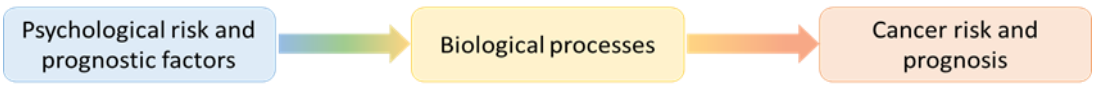


Figure 1: Linear model of the relationship between psychological factors on cancer

In order to propose a model that could explain those discrepancies, we proposed to introduce a new variable: the vagal nerve. Thus, we presented its relationships with psychological factors, biological mechanisms, and cancer prognosis. We conduct two studies to understand its role in cancer onset and its relationship with cancer risk factors (figure 9 below).

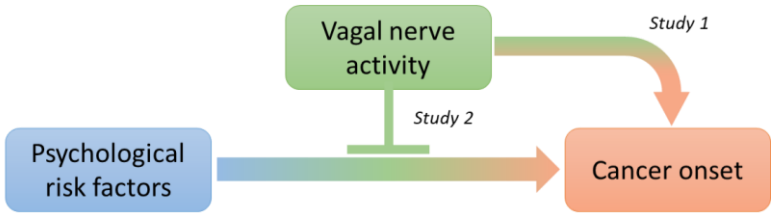


Figure 9: Modelisation of the possible role of the vagal nerve activity in cancer onset

3.1. PREDICTIVE ROLE OF VAGAL NERVE ACTIVITY

Cancer is a multifactorial disease, therefore cancer risk results from the interaction of several risk factors, which contribute to the complexity of cancer prevention. Thus, identifying an objective measure that could reflect the overall risk of developing cancer would be a major advancement in the fight against cancer. In this context, we wondered about the value of HRV as a predictive factor for cancer onset. Indeed, the vagal nerve is associated with several risk factors, such as age, depression, anxiety, alcohol use and smoking (e.g., Cheng et al., 2022; Koch et al., 2019; Ralevski et al., 2019).

Our first study did confirm that vagal nerve activity (i.e., HRV) was a predictive factor for cancer onset but only for people above 40 years old. This result might be explained by the fact that cancer risk is higher above 40 years old due the build-up of risk factors and that HRV would reflect this global risk.

To understand this assumption it is important to consider the complex interplay between risk factors, to understand what we mean by reflecting the global risk. Indeed, we used the term “build-up of risks” which reflects an accumulation of risks. However, this

accumulation is more complicated than just the sum of risk factors. Concerning psychological risk factors, even if their role in cancer risk or prognosis is difficult to delineate, it is clear that psychological factors are not exclusive, but rather interrelated. For example, while poor diet and low physical activity are both risk and prognostic factors, the combination of both may lead to high body mass index which is also a risk factor of cancer (Furer et al., 2020). Adding to this complexity, psychological factors may also interact with other risk factors, such as environmental one. Moreover, factors may also have an additive or multiplicative effect, meaning that the final effect of having several risk factors is higher than the sum of the effect of each one. For example, people who smoke and have been exposed to asbestos have a much higher risk to develop lung cancer (Suraya et al., 2020). Finally, one factor can lead to another factor, for example, because of apathy, which is one of the main symptoms of depression, patients may reduce their physical activity (Roshanaei-Moghaddam et al., 2009), leading to further risk of cancer. Also, since patients are more at risk to self-medicate in depression or anxiety, they may abuse substances such as alcohol or cigarettes (e.g., Lovell et al., 2015; Walsh et al., 2013). All of the risk factors mentioned above could influence vagal nerve activity. Additionally, in this thesis we focused on psychological risk factors, however, there is many other risks factors, such as environmental or genetic factors which are also part of the complex interplay between risks factors and may influence vagal nerve activity.

Moreover, even if did not discuss about protective factors in this thesis, they have to be taken in consideration when thinking about an overall risk indicator. Indeed, while low HRV is associated with risk factors (e.g., low physical activity), high HRV is associated with protective factors (e.g., healthy diet). Thus, we consider that HRV would be an indicator of the overall risk of cancer by reflecting the complex interplay between risks factors as well as the balance between risk and protective factors.

To summarize, our study has demonstrated the predictive role of HRV on cancer onset and we propose that HRV may be an indicator of the overall risk of cancer onset.

3.2. MODERATING ROLE OF THE VAGAL NERVE

Going further on the role of the vagal nerve, several studies shown that HRV moderates relationships between stress or brain activity with peripheral biological factors of importance in cancer (e.g., Ohira et al., 2013; Weber et al., 2010). As we introduce the vagal nerve in order to try to explain the discrepancies, one possibility was that the vagal nerve could be a moderator between psychological factors and biological mechanisms. Our results also confirm this hypothesis, indeed, LTE as a psychological variable did predict cancer onset only for participants with low HRV. Which suggest a moderating role of HRV over psychological factors, and more precisely, a protective role.

As explained previously, the interplay between risks factors is complex. In consequence, we may wonder whether the predictive role of LTE in people with low HRV does actually reflect a moderation from the vagal nerve or whether it reflect the interaction between LTE and other risks factors, which result in a low HRV. However, one way or the other, this result reflect a protective role of the vagal nerve. Nevertheless, it is important to explore those two possible role and try to understand if those roles may co-exist.

3.3. PREDICTIVE FACTOR OR MODERATOR

Our results regarding the relationships between HRV, age, LTE and cancer onset lead us to wonder whether HRV is an indicator and/or a moderator. Indeed, our first study suggests that HRV is a predictor of cancer onset while our second study suggests that HRV would be a moderator between psychological risk factors and cancer onset.

In order to make sense to those results, we went back to our second study. While alcohol consumption and BMI were both significant predictor of cancer in univariate

analyses, they were not in the multivariate analyses, not even for participants with low HRV. Thus, we found no moderator effect of HRV on alcohol, or BMI. Therefore, we could wonder whether the vagal nerve could actually have different role according to the risk factors considered. The first main difference we found about our variables was that some of them are modifiable (e.g., drinking alcohol) while others were not (e.g., having experienced LTE, personality trait). Thus, having high vagal nerve activity could moderate the effect of non-modifiable risk factors while the predictive role of the vagal nerve could concern modifiable variables such as depression, anxiety or actual health behavior. . Interestingly, those two models actually reflect the complex interplay between psychological factors. Indeed, modifiable factors (e.g., anxiety) could actually result from non-modifiable ones (e.g., LTE).

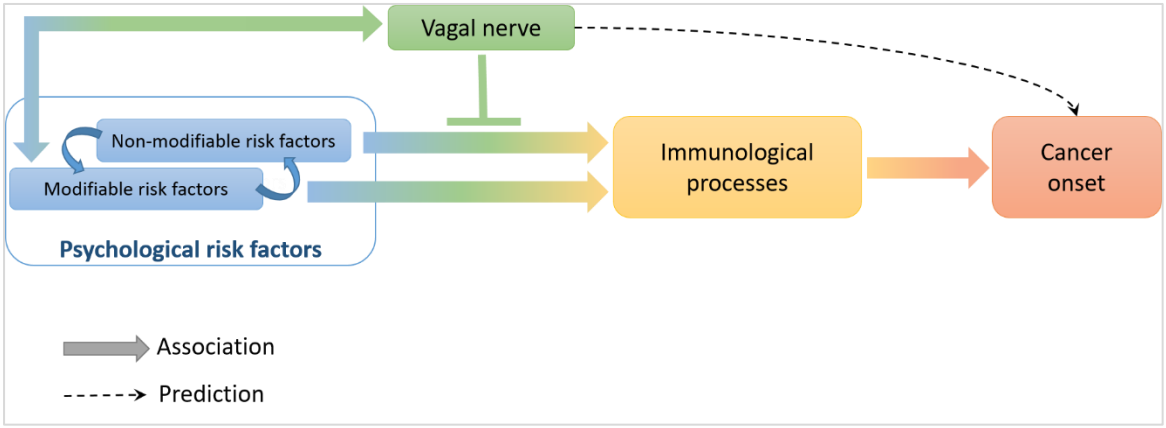
To summarize, two models would be possible depending on the variables. However, in both HRV may be considered as an objective measure of the overall cancer risk and consequently as a therapeutic target as high HRV would be associated with low cancer risk and low HRV associate with high cancer risk.

3.4. TOWARD A MORE COMPLEX MODEL

This thesis introduces the vagal nerve as a new element to understand the complex relationship between psychological factors and cancer onset. The linear model introduced at the beginning of this work did not take into consideration variability. Thus, we introduced the vagal nerve and we presented its relationships with psychological factors, biological mechanisms, and cancer onset in order to explain discrepancies. Vagal nerve activity (i.e., HRV) is associated with many risk and prognostic factors such as age, depression, anxiety, alcohol use and smoking (Koch et al al., 2019; Ralevski et al. 2019; Maurgia et al. 2019; Cheng et al. 2022). Moreover, the vagal nerve is involved in the neuro-immune axis as it

regulates the sympathetic system and the immune system through several pathways (e.g., Bonaz et al. 2017). Besides, HRV is associated with cancer prognosis (e.g. Zhou et al. 2016) and this relationship has been found to be mediated by inflammation in pancreatic cancer (De Couck et al. 2016). Finally, several studies show that HRV moderates relationships between stress or brain activity with peripheral biological factors of importance in cancer (e.g., Ohira et al., 2013; Weber et al., 2010). Regarding cancer onset, our studies have shown that HRV is a predictor of cancer onset and a moderator of non-modifiable

Figure 10: Psycho-Neuro-Biological model of cancer onset



psychological risk factors (i.e., LTE) on cancer onset. Thus, we propose a psycho-neuro-biological model of cancer onset that allows considering all these elements (figure 10).

With this model, we propose that vagal nerve activity could be an indicator of the overall risk of cancer onset. Moreover, in psychology, HRV is used as a measure of adaptability, this model propose the vagal nerve activity as a measure of adaptability in a physiologic way in respect of cancer. It reflects the capacity of the body to cope with psychological risk factors in order to protect itself from diseases. Consequently, the vagal nerve appears to be a relevant target for cancer prevention.

In conclusion, this thesis has attempted to understand the complex relationship between psychological risk factors and cancer development by proposing the vagal nerve

as a third variable to explain the discrepancies regarding this relationship. However, while we manage to answer our research question, new ones were raised. The following section discusses the limitations of this work as well as future directions to address most of these emerging questions.

4. LIMITATIONS AND FUTURE DIRECTIONS

The main limitations of our studies have been addressed in the discussion section of each study. Briefly, the limitations of the first two studies include its retrospective (pseudo-prospective) design, the brief ECG measure used to obtain HRV and the use of the LTE questionnaire not including subjective appraisal of event-severity. Regarding our experimental study, the limitations are the sample including healthy young adults and the short time lap between breathing exercises and the post-test measure of HRV. Future studies need to replicate our findings concerning HRV and cancer risk with longer ECG measures and prospective designs. The experimental study needs to be replicated with longer follow-ups of measuring HRV following different breathing patterns.

In order to replicate our results, and test our model, a longitudinal study need to be done. Regarding cancer onset, we need to confirm the relationship between psychological risk factors, HRV and cancer onset in a longitudinal design study with at risk people. A longitudinal study would allow us to include several psychological factors. First, information on current and past mental health, such as depression, anxiety, post-traumatic stress but also assessments of emotional regulation abilities or personality traits. Then, information on health behaviors such as diet, drinking, smoking or physical activity habits. We would also be able to obtain some relevant medical information (e.g., previous diseases considered as risk factor for cancer, family background). Moreover, it would allow us to realize longer ECG recording in order to obtain both time and frequency domain index of

HRV. Furthermore, to test our model in cancer prognosis similar study need to be conducted with patients.

Regarding the relationship between psychological factors, vagal nerve and biological processes, interdisciplinary study need to be done. In general, population, one way to explore those relationships would be to induce psychological changes in order to observe the effect on both vagal nerve and biological marker. As highlighted in Chapter 1, many psychological factors such as depression or anxiety, will lead to chronic stress, thus a stress induction paradigm would be relevant to assess both changes in HRV and salivary cortisol level. To induce stress in participants using the sing a song stress test (Brouwer & Hogervorst, 2014) or individualized audio recorded stress script (e.g., Higley et al., 2011). This would allow us to explore the relation between the stress level they express (i.e., appraisal), autonomic response (i.e., vagal nerve activity) and biological response (i.e., cortisol level).

Finally, in order to confirm the therapeutic interest of the vagal nerve in cancer prevention and management, the main direction would be to test the effect of slow-paced breathing in randomized control trial (RCT). However, in order to propose the most relevant breathing exercise training in such RCT, preliminary studies are needed. First, we have to compare the effect of SPB at 0.08Hz to SPB at the resonant frequency of participants, which imply to measure and determine their resonant frequency. Then, breathing exercises will have to be tested in general population with a sample of participants aged between 40 and 65 years old. Moreover, we will need to explore the effect of both exercises' duration (i.e., 5, 15 or 30minutes) and training frequency (i.e., twice a day, once a day or every other day practice) on the long-term effect of breathing exercise intervention.

Once all the variables regarding breathing exercise training will be known on general population, a longitudinal interventional study might be propose to participant at risk of cancer, in order to assess the efficacy of behavioral vagal nerve stimulation on cancer onset. At last, similar study will have to be conduct with cancer patients in order to test the efficacy of the breathing exercises training on patient prognosis.

To conclude, other aspects that have not being discussed in this thesis are very important for cancer care: side effect management and quality of life. Indeed, beyond patient prognosis, we are also particularly interested in the quality of life of patients. And the vagal nerve could be an important target to improve patient quality of life as it is associated with related variables such as psychological distress (e.g., H. G. Kim et al., 2018; Koch et al., 2019), cognitive function (Brouwer & Hogervorst, 2014) and physical symptoms such as pain (Caton et al., 2021) or nausea (Fletcher et al., 2008).

At this point, the future directions are mostly for research as our model still needs to be improved and testes. However, the clinical implications of this work are very important. Indeed, vagal nerve activity could be an important non-invasive, easy to obtain, measure to facilitate the screening in cancer risk, and its activation though behavioral intervention may help in cancer prevention and treatment. Thus, clinical implications of this work would have a huge contribution for global public health.

CONCLUSION

As a multifactorial disease, cancer results from the interaction of several factors, which contributes to the complexity of cancer prevention. In order to understand this complexity and to be able to identify a common factor, we focused on the vagal nerve and investigated the relationship between psychological risk factors, vagal nerve activity and cancer risk.

Our first study is, to the best of our knowledge, the first one to present the predictive role of vagal nerve activity in cancer onset. Moreover, we highlight the moderating role of the vagal nerve and thus its protective role against non-modifiable psychological risk factors. These results provide a glimpse of the therapeutic potential of the vagal nerve. Therefore, we explored the effect of slow-paced breathing exercises on HRV and shown that even if breathing exercises based on a 0.08Hz frequency are the most effective to increase HRV, every exercises between 0.07 and 0.1Hz lead to a significant increase. In other words, behavioral interventions based on breathing exercises, could be relevant to moderate the effect of non-modifiable psychological risk factors and prevent cancer onset.

Although our results represent a major step forward in cancer prevention, they open new perspectives for the management of non-modifiable risk factors and a whole field of investigations. Indeed, to apply those results and develop an effective behavioral intervention based on breathing exercises to improve HRV and thus prevent cancer, many studies remain to be conducted.

RESUME SUBSTANCIEL EN FRANCAIS

1. INTRODUCTION

À l'échelle mondiale, le Centre International de Recherche sur le Cancer (CIRC) estime à plus de 19 millions le nombre de nouveaux cas de cancer en 2020. Le cancer est une maladie multifactorielle et résulte de l'interaction entre plusieurs facteurs de risque. Pour l'Organisation Mondiale de la Santé (OMS), entre 30 et 50 % de ces cancers pourraient être évités en limitant les facteurs de risque évitables et en mettant en œuvre des stratégies de prévention. De même, la compréhension des facteurs pronostiques est cruciale pour réduire la mortalité. En effet, le CIRC a estimé que le cancer causait encore jusqu'à 10 millions de décès en 2020. Bien que des progrès importants aient été réalisés dans la prévention de la maladie et la prise en charge des patients, le cancer reste l'une des principales causes de décès et d'invalidité dans le monde (OMS, 2020).

En tant que maladie multifactorielle, le cancer résulte de l'interaction de plusieurs facteurs, tels que des facteurs psychologiques, environnementaux ou génétiques. Cela contribue à la complexité de la prévention du cancer. Afin de comprendre cette complexité et identifier un facteur commun, nous nous sommes concentrés sur le nerf vague et avons étudié la relation entre l'activité du nerf vague, les facteurs de risque et le risque de cancer.

Afin d'expliquer pourquoi cette thèse s'intéresse au nerf vague et à sa relation avec le cancer, la première partie, l'introduction théorique, est composée de trois chapitres. Le premier présente les mécanismes biologiques de base conduisant au développement du cancer, les facteurs de risque et de pronostic et la relation entre ces facteurs et le développement du cancer. Le deuxième chapitre concernera le nerf vague, son activité, sa relation avec le développement du cancer et les facteurs de risque et de pronostic du cancer.

Enfin, le dernier chapitre présente le raisonnement, les objectifs et les hypothèses de cette thèse.

La deuxième partie de cette thèse est empirique et comprend la présentation des études menées. Les deux premiers sont des analyses de bases de données et le dernier chapitre est une étude expérimentale originale. Le premier chapitre met en évidence le rôle prédictif de l'activité du nerf vague dans l'apparition du cancer, le second souligne le rôle modérateur de l'activité du nerf vague entre les événements menaçants et l'apparition du cancer. Enfin, le dernier chapitre est une étude comparative de plusieurs exercices respiratoires visant à augmenter l'activité du nerf vague.

La dernière partie de la thèse sera la discussion générale. Nous résumerons d'abord les principaux résultats, puis nous discuterons des résultats de ces études, c'est-à-dire que nous aborderons leurs limites et aurons une discussion complète de nos résultats afin de les clarifier et de souligner leurs contributions. Ensuite, nous proposerons un modèle pour illustrer les relations entre les facteurs psychologiques et le cancer. Enfin, nous développerons nos orientations futures.

2. CADRE THEORIQUE

Dans le premier chapitre, nous avons mis en évidence la relation entre le développement du cancer, les mécanismes biologiques et les facteurs psychologiques. Nous avons présenté certains des mécanismes biologiques les plus pertinents impliqués dans le développement du cancer, à savoir les mutations de l'ADN, la croissance cellulaire et l'implication des systèmes immunitaire et nerveux dans le développement du cancer. Nous avons documenté les effets des facteurs psychologiques de risque et de pronostic dans certains mécanismes, tels que les effets cancérigènes, l'augmentation de l'inflammation ou

l'activité sympathique excessive. Tout au long de ce chapitre, nous avons vu l'importance de l'axe neuro-immunitaire dans le développement du cancer.

Dans le deuxième chapitre de cette thèse, nous avons mis en évidence l'implication du nerf vague dans le développement du cancer. Tout d'abord, son implication dans la régulation de l'axe neuro-immunitaire. Puis, nous avons présenté les nombreuses associations observées entre le nerf vague, les facteurs psychologiques, le développement du cancer et le pronostic du cancer. Ce chapitre met l'accent sur la place centrale du nerf vague dans le développement du cancer.

Ces deux chapitres ont mis en évidence ce que nous savons, mais aussi ce que nous ne savons pas encore. En effet, des facteurs de risque et de pronostic, tels que les événements menaçants et le tabagisme, sont associés d'une part au risque de cancer et au pronostic, et d'autre part à l'activité du nerf vague. De plus, les mécanismes impliqués dans le développement du cancer sont les mêmes qui expliquent l'impact des facteurs de risque et de pronostic dans le cancer, et sont également liés au nerf vague (par exemple, l'inflammation). Alors que l'activité du nerf vague (VRC) a été reconnue comme un facteur indépendant de pronostic du cancer chez les patients (De Couck et al., 2018 ; Zhou et al., 2016), nous pourrions nous demander si l'activité du nerf vague pourrait être un indicateur de risque d'apparition du cancer. Une telle découverte serait importante pour la prévention de l'apparition du cancer et pour la détection précoce. En effet, ce sont deux leviers importants pour réduire le poids du cancer dans le monde. De plus, comme expliqué dans cette section théorique, le cancer résulte de l'interaction de plusieurs facteurs, ce qui contribue à la complexité de la prévention du cancer. Ainsi, l'identification d'une mesure objective qui pourrait refléter le risque global de développer un cancer constituerait une avancée majeure dans la lutte contre le cancer.

En plus d'être un prédicteur potentiel de l'apparition du cancer, on peut se demander si le nerf vague peut également modérer (augmenter ou diminuer) les effets des facteurs psychologiques sur le développement du cancer. En effet, les effets des facteurs psychologiques sur les mécanismes biologiques sont principalement expliqués par l'activité du système nerveux autonome. Par conséquent, le nerf vague est impliqué dans la façon dont les facteurs de risque psychologiques peuvent avoir un impact sur le développement du cancer, par exemple via l'inflammation. Dans des études antérieures, le VRC a modéré les effets du stress sur les résultats biologiques (Weber et al., 2010) et a modéré les relations entre l'activité cérébrale et l'immunité périphérique anti-tumorale (Ohira et al., 2013). Ainsi, nous nous sommes demandés si le nerf vague pouvait être un modérateur dans la relation entre les facteurs de risque psychologiques et le risque de développer un cancer. Même si certaines études explorent l'impact des événements menaçants sur l'apparition du cancer du sein, du cancer colorectal et du cancer du poumon, à notre connaissance, l'impact de ces événements sur l'apparition du cancer (tous cancers confondus) n'a pas encore été pleinement exploré. Ainsi, nous avons souhaité tester le rôle modérateur du nerf vague dans la relation entre les événements menaçants et l'apparition du cancer.

Enfin, une faible activité du nerf vague est associée à des facteurs de pronostic psychologique, et à un pronostic plus défavorable des patients atteints de cancer. En outre, les exercices de respiration peuvent être mis en œuvre dans le cadre des soins du cancer (par exemple, Fournié et al., 2022 ; Hasuo et al., 2020) et augmenter le VRC (Laborde et al., 2021). Ainsi, la stimulation du nerf vague par la respiration pour améliorer le pronostic des patients ou réduire le risque de cancer, pourrait revêtir une importance considérable. Cependant, malgré des résultats encourageants concernant la respiration et l'activation du nerf vague, il faut noter qu'il y a un manque d'études méthodologiques sur lesquelles s'appuyer pour développer de telles interventions.

3. PARTIE EMPIRIQUE

L'objectif général de cette thèse est de comprendre le rôle du nerf vague dans l'apparition du cancer et de caractériser sa relation avec les facteurs de risque de cancer. L'intérêt clinique ultime est d'introduire à terme le nerf vague comme cible thérapeutique dans la prévention et la prise en charge du cancer. Pour répondre à cet objectif, nous avons souhaité répondre à plusieurs questions :

1- L'activité du nerf vague permet-elle de prédire la survenue d'un cancer ? (Etude 1)
2- Le nerf vague modère-t-il la relation entre les facteurs psychologiques et le risque de développer un cancer ? (Etude 2)
3- Quel est le meilleur exercice respiratoire pour améliorer l'activité du nerf vague ? (Etude 3)

Pour répondre à ces objectifs, nous avons réalisé trois études (voir figure 8), qui constituent la partie empirique de cette thèse. Les études 1 et 2 sont des études longitudinales rétrospectives. La première étude visait à explorer le rôle prédictif de l'activité du nerf vague dans l'apparition du cancer. La deuxième étude s'est concentrée sur le rôle modérateur du nerf vague concernant le rôle des facteurs de risque psychologiques dans l'apparition du cancer. Enfin, la troisième étude, de type expérimental, a testé si différents exercices de respiration pouvaient augmenter l'activité du nerf vague - VRC.

3.1. Etude 1

Le premier objectif était d'explorer le rôle prédictif de l'activité du nerf vague dans l'apparition du cancer. Dans le deuxième chapitre, nous avons souligné que l'activité du nerf vague est associée au pronostic du cancer ; une faible activité prédit une moins bonne survie. De plus, les facteurs de pronostic et les facteurs de risque sont associés à l'activité du nerf vague et le nerf vague inhibe des processus biologiques cruciaux, qui contribuent à

l'oncogenèse. Nous avons donc cherché à savoir si un faible VRC pouvait être un facteur de risque d'apparition d'un cancer. Notre hypothèse était qu'une faible activité du nerf vague, mesurée par le VRC, permettrait de prédire un risque plus élevé d'apparition d'un cancer.

Pour vérifier cette hypothèse, nous avons utilisé une étude longitudinale basée sur une grande cohorte. Nous avons donc effectué une réanalyse en utilisant des données existantes - la cohorte Lifelines (voir chapitre 4). La cohorte Lifelines est une cohorte longitudinale qui a suivi plus de 167 000 participants sur une période de 30 ans aux Pays-Bas. Nous avons inclus 82 768 participants (59,2 % de femmes) qui n'avaient pas de cancer au départ. Leur activité du nerf vague au début de l'étude a été indexée par le paramètre VRC du RMSSD obtenu à partir d'ECG brefs. L'apparition du cancer a été signalée lors d'une seconde évaluation, 5 ans plus tard.

3.2. Etude 2

Le deuxième objectif était d'explorer le rôle modérateur du nerf vague. En effet, dans le premier chapitre nous avons expliqué que les effets des facteurs psychologiques sur les mécanismes biologiques, qui sont principalement expliqués par l'activité du système nerveux autonome, tandis que dans le deuxième chapitre nous avons présenté le rôle protecteur du nerf vague. De plus, des études antérieures ont également montré que l'activité vagale modère les effets du stress sur l'organisme (Weber et al., 2010) et qu'elle est un modérateur entre l'activité cérébrale et l'immunité au cancer (Ohira et al., 2013). Par conséquent, le nerf vague pourrait être impliqué dans la façon dont les facteurs de risque psychologiques affectent le développement du cancer. Nous avons donc cherché à vérifier si le nerf vague pouvait être un modérateur dans la relation entre les facteurs de risque psychologiques et l'apparition du cancer (2). Par conséquent, notre hypothèse était qu'une

activité plus élevée du nerf vague modérerait la relation entre les facteurs de risque psychologiques (événements menaçants) et l'apparition du cancer.

Pour tester cette hypothèse, nous avons utilisé la même base de données : la cohorte Lifelines, afin d'effectuer une analyse longitudinale (voir chapitre 5). Parmi les autres variables psychologiques, nous avons décidé d'utiliser le score des événements menaçant évalué au départ. Nous avons utilisé le RMSSD comme indice de l'activité du nerf vague au départ et l'apparition du cancer signalée lors de la deuxième évaluation 5 ans plus tard. Nous avons inclus le même échantillon de 82 768 participants exempts de cancer au départ, comme dans l'étude 1.

3.3. Etude 3

Enfin, notre troisième objectif était de tester les effets des exercices de respiration sur la VRC. Plus précisément, nous souhaitions tester quel modèle de respiration serait le plus efficace pour améliorer l'activité du nerf vague - VRC. Étant donné qu'une faible activité du nerf vague est associée à des facteurs de pronostic psychologique défavorables, à des mécanismes étiologiques biologiques du cancer et à un pronostic plus défavorable du cancer, nous nous sommes demandé s'il était possible d'augmenter l'activité du nerf vague de la manière la plus efficace, afin de réduire le risque de cancer et d'améliorer le pronostic (3). Cependant, il n'y a pas encore de preuves claires utilisant une méthodologie stricte concernant le modèle de respiration qui augmente le plus efficacement la VRC. D'autre part, il existe une grande variété entre les différents schémas respiratoires utilisés pour améliorer l'activité du nerf vague. Compte tenu de ces multiples sources de données, notre objectif était de comparer, dans le cadre d'un plan expérimental strict, différents schémas respiratoires et leur effet sur la VRC pendant et après l'exercice respiratoire.

Nous avons conçu un plan d'étude expérimental (voir chapitre 6) pour tester cette question. Nous avons recruté 107 participants, qui ont été répartis au hasard dans l'un des 9 modèles d'exercice respiratoire. Les données de 105 participants (21 hommes, tranche d'âge = 18-32 ans, M = 21,38, SD = 3,20 ans) ont été analysées. La fréquence cardiaque et le VRC ont été enregistrés pendant toute la durée de la tâche. Ensuite, pour chaque exercice de respiration, nous avons comparé les niveaux de VRC pendant l'exercice avec les niveaux de VRC pré-test entre les 9 modèles de respiration afin de tester les effets des différents modèles de respiration sur la VRC post-test.

4. RESULTATS

L'objectif général de cette thèse est de comprendre le rôle du nerf vague dans l'apparition du cancer et de caractériser sa relation avec les facteurs de risque de cancer. Nous avons mis en évidence que les facteurs de risque et de pronostic sont similaires pour l'apparition et le pronostic, que le nerf vague est lié à ces facteurs, à la régulation des processus impliqués dans le développement du cancer et que son activité peut être considérée comme un facteur pronostique. Malgré ces facteurs et mécanismes communs, la majorité de la littérature s'est principalement concentrée sur le VRC et le pronostic du cancer, laissant son rôle dans l'apparition du cancer sous-examiné.

Nous avons donc exploré le rôle prédictif du VRC dans l'apparition du cancer (étude 1), afin de répondre à notre première hypothèse : l'activité du nerf vague (VRC) permet-elle de prédire l'apparition du cancer ? Sur la base d'un ensemble de données prospectives, nous avons constaté que la VRC était effectivement un facteur prédictif de l'apparition d'un cancer, mais uniquement chez les personnes âgées de plus de 40 ans.

En outre, plusieurs études suggèrent un rôle modérateur de l'activité du nerf vague. Par exemple, elle modère l'association entre l'activité cérébrale et les réponses immunitaires

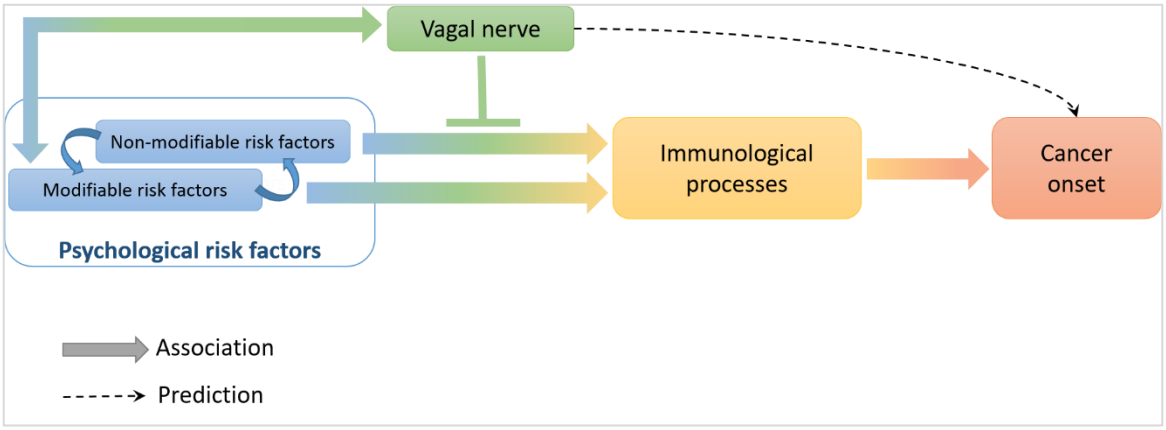
dans les situations de stress aigu (Ohira et al. 2013) et modère les effets du stress aigu sur l'organisme (Weber et al., 2010). Ainsi, nous avons décidé de mener une autre étude pour explorer le rôle modérateur de l'activité du nerf vague dans la relation entre les facteurs psychologiques et l'apparition du cancer (étude 2) et répondre à notre deuxième hypothèse : le nerf vague modère-t-il la relation entre les facteurs psychologiques et l'apparition du cancer ? Dans cette étude, nous avons testé notre deuxième hypothèse sur les événements mettant la vie en danger et l'apparition du cancer et nous avons constaté que l'activité du nerf vague est un facteur de protection contre l'effet des événements mettant la vie en danger sur l'apparition du cancer.

L'effet modérateur du nerf vague sur ce facteur de risque nous a encouragés à explorer le nerf vague comme une cible thérapeutique potentielle dans la prévention et la gestion du cancer. Les exercices de respiration constituent une intervention comportementale permettant d'atteindre cet objectif. Cependant, en raison de résultats contradictoires concernant l'efficacité des techniques de respiration, nous avons décidé de mener une étude expérimentale originale afin d'explorer les effets de différents exercices de respiration sur le VRC en contrôlant la fréquence et le modèle. Ainsi, dans une troisième étude (étude 3), nous avons exploré l'efficacité de plusieurs exercices de respiration afin de répondre à notre dernière hypothèse : quel est le meilleur exercice de respiration pour améliorer l'activité du nerf vague ? Nous avons constaté que l'efficacité des exercices respiratoires dépend de leur fréquence respiratoire. En effet, alors que chaque fréquence (0.1, 0.08 et 0.07 Hz) conduit à une augmentation significative de la VRC, la plus grande augmentation a été trouvée pour les exercices respiratoires de 0.08 Hz pour la RMSSD et pour les deux 0.08 et 0.07 Hz pour la LF-HRV. De plus, nous avons constaté qu'une VRC faible avant l'exercice respiratoire était associée à une augmentation plus importante pendant l'exercice. En revanche, les modèles d'exercices n'ont pas affecté l'efficacité des exercices.

5. DISCUSSION

Cette thèse introduit le nerf vague comme un nouvel élément pour comprendre la relation complexe entre les facteurs psychologiques et l'apparition du cancer. Le modèle linéaire introduit au début de ce travail ne prenait pas en compte la variabilité. Ainsi, nous avons introduit le nerf vague et nous avons présenté ses relations avec les facteurs psychologiques, les mécanismes biologiques et l'apparition du cancer afin d'expliquer les divergences. L'activité du nerf vague (c'est-à-dire la VRC) est associée à de nombreux facteurs de risque et de pronostic tels que l'âge, la dépression, l'anxiété, la consommation d'alcool et le tabagisme (Koch et al., 2019 ; Ralevski et al. 2019 ; Maurgia et al. 2019 ; Cheng et al. 2022). En outre, le nerf vague est impliqué dans l'axe neuro-immunitaire car il régule le système sympathique et le système immunitaire par plusieurs voies (par exemple, Bonaz et al. 2017). En outre, le VRC est associé au pronostic du cancer (par exemple, Zhou et al. 2016) et il a été constaté que cette relation est médiée par l'inflammation dans le cancer du pancréas (De Couck et al. 2016). Enfin, plusieurs études montrent que la VRC modère les relations entre le stress ou l'activité cérébrale avec des facteurs biologiques périphériques importants dans le cancer (par exemple, Ohira et al., 2013 ; Weber et al., 2010). En ce qui concerne l'apparition du cancer, nos études ont montré que la VRC est un prédicteur de l'apparition du cancer et un modérateur des facteurs de risque psychologiques non modifiables (c'est-à-dire la LTE) sur l'apparition du cancer. Ainsi, nous proposons un modèle psycho-neuro-biologique de l'apparition du cancer qui permet de considérer tous ces éléments (figure 10).

Figure 20: Psycho-Neuro-Biological model of cancer onset



Avec ce modèle, nous proposons que l'activité du nerf vague puisse être un indicateur du risque global d'apparition du cancer. De plus, en psychologie, le VRC est utilisé comme une mesure de l'adaptabilité, ce modèle propose l'activité du nerf vague comme une mesure de l'adaptabilité de manière physiologique en ce qui concerne le cancer. Elle reflète la capacité de l'organisme à faire face aux facteurs de risque psychologiques afin de se protéger des maladies. Par conséquent, le nerf vague semble être une cible pertinente pour la prévention du cancer.

6. CONCLUSION

En conclusion, cette thèse a tenté de comprendre la relation complexe entre les facteurs de risque psychologiques et le développement du cancer en proposant le nerf vague comme troisième variable pour expliquer les divergences concernant cette relation. Cependant, si nous parvenons à répondre à notre question de recherche, de nouvelles questions ont été soulevées.

En tant que maladie multifactorielle, le cancer résulte de l'interaction de plusieurs facteurs, ce qui contribue à la complexité de la prévention du cancer. Afin de comprendre cette complexité et de pouvoir identifier un facteur commun, nous nous sommes concentrés

sur le nerf vague et avons étudié la relation entre les facteurs de risque psychologiques, l'activité du nerf vague et le risque de cancer.

Notre étude est, à notre connaissance, la première à présenter le rôle prédictif de l'activité du nerf vague dans l'apparition du cancer. De plus, nous mettons en évidence le rôle modérateur du nerf vague et donc son rôle protecteur vis-à-vis des facteurs de risque psychologiques non-modifiables. Ces résultats permettent d'entrevoir le potentiel thérapeutique du nerf vague. Nous avons donc exploré l'effet d'exercices respiratoires à rythme lent sur le VRC et montré que même si les exercices respiratoires basés sur une fréquence de 0,08Hz sont les plus efficaces pour augmenter le VRC, tous les exercices entre 0,07 et 0,1Hz conduisent à une augmentation significative. En d'autres termes, les interventions comportementales basées sur les exercices de respiration pourraient être pertinentes pour modérer l'effet des facteurs de risque psychologiques non-modifiables et prévenir l'apparition du cancer.

Bien que nos résultats représentent une avancée majeure dans la prévention du cancer, ils ouvrent de nouvelles perspectives pour la gestion des facteurs de risque non-modifiables et tout un champ d'investigations. En effet, pour appliquer ces résultats et développer une intervention comportementale efficace basée sur des exercices de respiration pour améliorer le VRC et ainsi prévenir le cancer, de nombreuses études restent à mener.

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APPENDICES

APPENDIX 1: ETHICAL APPROVAL

Université de Lille

Comité d'éthique en sciences comportementales

Présidente :
Yvonne DELEVOYE-TURRELL

Président adjoint :
Cédric PATIN

Gestionnaire administrative :
Stella BOUAMRIRENE
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Villeneuve d'Ascq, le 30/04/2020

Références comité d'éthique :	2020-415-S81
Sigle :	**RespiRate**
Numéro de version et date :	**Version 2 du 30/04/2020**
Promoteur :	**Delphine GRYNBERG**
Responsable Scientifique du projet : ULille-SHS-ALL	

Date de la soumission :

Avis du Comité d'Ethique : Avis favorable.

Le protocole est accepté en état. Si pour une quelconque raison, vous souhaitez modifier le protocole (en terme de calendrier, inclusion d'un nouveau groupe…), vous êtes tenu d'informer le comité d'éthique par l'envoi d'un avenant expliquant les motivations mais également les modifications apportées au protocole initial. Cet avenant sera réévalué par le comité d'éthique.

L'avis du CER-Lille n'exonère pas des formalités réglementaires. A cet égard, il vous appartient notamment, si vous traitez des données se rapportant à un individu directement ou indirectement identifiable, de vous conformer au règlement européen sur la protection des données (RGPD) en vigueur depuis 2018. Pour cela, vous pouvez solliciter les conseils du Correspondant informatique et libertés (DPO) ou du service juridique de votre université ou de votre organisme de recherche.

Pr Yvonne DELEVOYE-TURRELL
Présidente du comité d'éthique

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APPENDIX 2: SCIENTIFIC CONTRIBUTIONS

PUBLICATIONS

Caton, L., Bolzon, M., Boschiero, D., Thayer, J. F., & Gidron, Y. (2021). Pre-surgical heart-rate variability strongly predicts less post-operative pain in patients with epilepsy. *Journal of Psychosomatic Research*, *145*, 110421.

Gidron, Y., **Caton, L.**, & Reich, M. (2019). Stress, Inflammation and Cancer Prognosis: New Evidence-Based Effective Treatments. *Psycho-Oncologie*, *13*(3-4), 150-155.

ORAL COMMUNICATION

Caton, L. & Gidron, Y. (2022, August). Vagal nerve activity moderates relationships between life events and cancer onset: making things less vague. 36th Annual Conference of the European Health Psychology Society, Bratislava, Slovakia.

POSTER

Caton, L., Vlemincx, E., Gidron, Y., Grynberg, D. (2021, August) How to increase heart rate variability based on breathing exercises? 35th Annual Conference of the European Health Psychology Society, Online.

Caton, L., Vlemincx, E., Gidron, Y., Grynberg, D. (2021, July). Impact of breathing exercises on HRV: effect of frequency and pattern. 5th International conference of the European Society for Cognitive and Affective Neuroscience, Online.