# Correlations between Homoeostatic Reserve and Mortality in Cancer: A Literature Review

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**Submission:** October 31, 2017; **Published:** December 08, 2017

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### Abstract

This paper reviews the literature regarding the correlations between homoeostatic reserves and mortality for cancer. We will review the literature about the use of bio-impedance assessment (BIA) and heart rate variability (HRV) to assess homoeostatic reserves. We know that in the different stages of cancer the functional reserves change significantly. During the treatment and after the treatment of cancer the level of the homoeostatic reserve is a measure of morbidity and mortality. One way of measuring the functional reserves of the body is by using the bio-impedance assessment (BIA) and heart rate variability (HRV) assessment. Both the bio-impedance assessment and heart rate variability assessment are independent markers for homoeostatic reserves. For BIA the key marker appears to be the phase angle (PhA). For HRV the key marker appears to be the balance of the autonomic nervous system (ANS)

**Keywords:** Cancer; Heart rate variability assessment; Bio-impedance assessment; PhA; ANS

**Abbreviations:** BIA: Bio-Impedance Assessment; HRV: Heart Rate Variability; PhA: Phase Angle; ANS: Autonomic Nervous System ; AD: Autonomic Dysfunction

## Introduction

### What is homoeostatic reserve?

Homeostatic reserve is defined as the redundancy of physiologic functions present in human systems that is used to overcome acute and chronic health insults. The frailty phenotype [1] can be used as a marker indicating a critical threshold in decline of homeostatic reserve. Decline in the homeostatic reserve has been hypothesized to be a contributing factor to progression of chronic disease states, development and worsening of geriatric syndromes, and decline in ability to perform activities of daily living [1,2]. Bioelectrical impedance analysis (BIA) is a simple, inexpensive, quick and non-invasive technique for measuring body composition and cell membrane function. The phase angle (PhA) in BIA provides a marker of the cell membrane function. Heart Rate Variability refers to the variation between the normal heart rate and a given mean value. Heart Rate Variability Assessment (HRV) can also be used to assess variation between the normal heart rate and a given mean value and autonomic dysfunction (AD).

As homoeostatic reserve declines, the individual in concern becomes increasingly unable to perform simple everyday duties, maintain appropriate blood pressure or balance, maintain healthy immunity to disease, modulate weight and so on [1]. This decline can be measured in many ways. Some of them include assessing the cell membrane function and autonomic dysfunction (AD). As such the state of the homeostatic reserve becomes one way of assessing the progression of physiological function in the case of cancer. Obviously as homoeostatic reserve declines it indicates that the organism's capacity to overcome the health insults due to cancer is reduced. When a critical threshold is reached, this decline becomes irreversible.

The phase angle (PhA) in BIA provides a marker of the cell membrane function. As the PhA declines, homoeostatic reserves can be said to be declining as well. For a long time, researchers have known that autonomic dysfunction (AD) causes death from heart disease and HRV analysis, which provides information about the autonomic nervous system (ANS) in various ailments [3-9]. HRV methods possess the ability to show the amount of dysfunction in ANS, brought about by disorders such as cancer. As the degree of AD increases homoeostatic reserves can be said to be declining as well. The focus is on two modes of monitoring the status: BIA and HRV

    A.    Variables involved in and those used to measure the BIA and HRV

B.     The impact of other variables like stress and disease on BIA and HRV as well as the relationship between these diseases and the changes in BIA and HRV

C.     The use of BIA and HRV in the management of stress and cancer as well as the impact of different attempts at modulation.

## Methods and Materials

A literature search was conducted using Pub Med, Medline and other databases for literature on the related topics to March 2016. The heading used was Bio-impedance and Cancer, Heart Rate Variability and Cancer. The search was limited to studies in the English language. It focused on clinical studies, clinical trials and reviews. Abstracts were screened and articles individually selected based on quality and focus of the study

## Introduction to BIA

Bioelectrical impedance analysis (BIA) is a simple, inexpensive, quick and non-invasive technique for measuring body composition. "Impedance" is a physical variable describing the resistance characteristics of an electrical circuit in the presence of an alternating current between electrodes located in a circumference surrounding the studied object. Thus, it reflects global opposition to the passage of current [10].

Using bioelectrical impedance analysis as a diagnostic tool to examine the electrical characteristics of tissues provides information on a non-invasive and continuous basis, at the patient bedside without need for radiological investigations. Mathematically, the bioelectrical impedance is represented as a complex number comprising a real component (resistance) and an imaginary dimension (reactance) [3]. The electrical impedance (Z) consists of two components, resistance (R) and reactance (Xc). Resistance is a measure of total body water and reactance a measure of body cell mass (BCM). From the determined impedance a number of BIA parameters can be estimated [11].

Body Cell Mass (BCM), consists of all cells that have an effect on metabolism (% BCM in FFM), extra cellular mass (ECM), extracellular water/fluid (ECW/ECF), fat-free mass (FFM), fat mass (FM), total body water (TBW) [12-15]. The impedance unit is the ohm (Ω), when this variable is applied to biological tissue we speak of "bio-impedance" [10]. In this context, it is very important to note that the biological tissues have complex electrical impedance. And that is dependent on the frequency of the electrical applied field and tissue cellular structure. Therefore, the electrical impedance of tissue is a function of its structure and it can be used to differentiate normal and cancerous tissues [16-18] in a variety of organs. Bio-impedance analysis could apply easily and routinely in the arm, trunk, and leg and from wrist to ankle.

One of the most important applications of the BIA is its use as a prognostic tool for overall survival, particularly for patients with severe cancers. In this concern, the phase angle (PhA), [19-22] is one of the most important indicators for predicting life quality and overall survival, particularly for cancer patients. Since, the phase angle provides a marker of cell membrane function, R0 and R∞ have been used to predict clinical outcome. (R0 is the resistive part at zero frequency (Ω), R∞ is the resistive part at infinite frequencies).

Physically, using of BIA method for characterizing different tissues is to fit data by the Cole equation models, which describe the behavior of permittivity and conductivity as a function of frequency. The commonly used circuit represents biological tissues activities, in which, the R of extracellular fluid is arranged in parallel to the second arm of the circuit "which consists of capacitance" and R of intracellular fluid in series. Resistive part (R) and capacitance can all be measured over a range of frequencies (most single frequency BIA analyzers operate at 50-kHz). At zero (or low) frequency, the current does not penetrate the cell membrane, which acts as an "insulator", and therefore the current passes through the extracellular fluid, which is responsible for the measured R of the body R0 . At infinite frequency (or very high frequency) the capacitor behaves as a perfect (or near perfect) capacitor, and therefore the total body R (R∞) reflects the combined of both intracellular and extracellular fluid. The impedance version is the Cole equation:

$$Z(\omega) = R\infty + R0 - R\infty$$

$$1 + (j\omega t)\alpha$$

Where, $Z(\omega)$ is the complex impedance in ohm (Ω), R0 is the resistive part at zero frequency (Ω), R∞ is the resistive part at infinite frequencies (Ω), t is a time constant, e.g., the mean relaxation time in a distribution of time constants, and α (p/2) is the constant phase angle, ω is the frequency (in rad s-1), the constant1-αmay also be viewed as describing the width of the distribution of time constants.

## Tissue identification and monitoring

Any changes in tissue physiology should produce changes in the tissue electrical properties [23]. Based on this phenomenon, BIA analysis has been widely used to identify or monitor the presence of various illnesses or conditions such as body fluid shift, blood flow, cardiac output, and muscular dystrophy [24-37]. Different tissues exhibit different electrical properties, in addition, tissue electrical properties change with respect to tissue status evolution. Thus it is easy to conceive that bio-impedance method can be applied to identify and monitor tissues. The bio-impedance method can be adopted for characterizing different tissues [25,26]. For instance, the lung tissues show a 5-fold greater electrical current resistance than the rest of the intrathoracic soft tissues [10]. During the cyclic breathing process, the impedance of the pulmonary tissues changes 5% in the context of calm breathing, and up to 300% when inhaling from residual volume to total lung capacity [38]. One of the most

attractive applications of bio-impedance characterization is cancer detection [29,34,39].

Hence, there are vast majority physiological differences in tumor tissues, thus BIA is efficiently applicable method for monitoring and distinguish normal healthy and tumor tissues. For instance tumors have much higher water content in their cells rather normal cells because of cellular necrosis and fenestrated vascularization and that will reflects on the tissue conductivity [16]. The cancerous tissues exhibit sharply different bioelectrical properties as compared with the normal tissues. The higher conductivity of tumors could lead to their selective targeting by radio frequency hyperthermia treatment [35]. In early stages of tumor a disturbance in the cellular water/electrolyte content, cell membrane permeability, and orientation/packing density of cells will occur. These changes and abnormalities will reflect on tissue impedance, which could be detected by using bio-impedance.

### Applications of Bia In health care, Medical diagnosis and quality of life

Obesity is a common nutritional problem in both developed and developing countries. In a cross-sectional study, the prevalence of being overweight and obese using both bioelectrical impedance analysis (BIA) and body mass index (BMI) has been investigated. A close correlation for BMI and obesity has been confirmed [40]. A variety of BIA studies have been done in evaluating body composition including FFM, BF and BCM in multiple population samples [41-47].

On the other hand, in a prospective study the usefulness of bio-impedance measurement have been investigated for predicting the treatment outcome in breast cancer related lymphedema (BCRL) patients [32,46]. In this study, the ratio of extracellular fluid (ECF) volume has been investigated by using bioelectrical impedance spectroscopy (BIS), and single frequency bio-impedance analysis (SFBIA) at a 5 kHz frequency before treatment[18,30,48-54].

They also investigated whether there is correlation between ECF ratio and SFBIA ratio with the change of arm circumference. The study concluded that ECF volume measurements and SFBIA before treatment are useful tools for predicting the outcome of patients with lymphedema [49,50,54]. Additionally, ECF volume measure can be used as a screening tool for predicting treatment outcome of BCRL patients [32]. There are lots of studies involved phase angle as a reliable predictive factor for quality of life and overall survival, particularly for cancer patients [55-58].

### Physiological parameters affecting bioelectrical impedance assessment accuracy

Although the fact that an increased conductivity may be used to identify the presence of tumors [59,60], there are lots of limitations for BIA metric analysis due to the complication and variation in the biological system [61]. Their important review by author Damijan et al. [16] discussed efficiently lots of problems of biological concern.

Relative to water, fat is a much poorer conductor of electricity, thus the changes in body fat and water balance will reflect on tissue impedance. Cell and tissue death also cause many irreversible changes including viscosity of the extra/intracellular fluids [62]. And promote changes in the mobility and distribution of ions which have the ability to transport the current. In the living physiological system, if the blood flow is interrupted, metabolism could continue in an anaerobic manner. That in turn, leads to an increase in the level of the extracellular fluid due to the osmotic pressure. Therefore, BIA when applied in such conditions, there is a false increase in the tissue impedance. Even, the brief decrease in the blood flow has an impact and could change tissue resistivity.

The respective figures are not absolute and can vary according to the conditions of the environment or medium (eg. temperature). A temperature increase is associated with a decrease in impedance [10], due to the prominent increase in ions mobility [63-65] that "transport the current", and decrease viscosity of the extracellular fluid. A general increase of about 2% occurs in the conductivity of tissue [33] in the frequency range below 1 GHz, up to a temperature of about 40°C. Above that point, the cell membrane begins to deteriorate and allows the cytosol to leak into the extracellular space. Nevertheless, the rapid increase of conductivity with temperature was suggested to be used to monitor the progress of hyperthermia treatment [66].

### Conclusion [67]

BIA works well in healthy subjects and chronic diseases with a validated BIA equation that is appropriate with regard to age, sex and race. The metric measurements includes: body mass index, fat-free mass, body fat, body cell mass, extracellular fluid, intracellular fluid, blood loss, and total body water [68]. Due to differences in growth velocity and puberty related changes Bio-impedance metric analysis interpretation in children is much more difficult. For instance, errors in estimation of fat mass using Bio-impedance analysis and Dual energy X-ray Absortiometry (DXA) can be very large, and the direction of error can differ between the sexes in children [40-42].

Furthermore, the Bio-impedance analysis device tested displayed poor individual accuracy for the estimation of body composition compared with a four compartment criterion method [43]. In this sense, it is very important to note that the use of segmental Bio-impedance analysis also requires further validation at increased temperature, edema and abnormal hydration. Thus, Bio-impedance analysis should be interpreted with caution until further validation has proven for Bio-impedance analysis algorithm to be accurate in such conditions.

The potential sources of errors for Bio-impedance analysis in some specific subjects may be due to increased bone mass of limbs and changes in skin thickness and hydration, which might influence the extension of the tissues electrical characteristics. The eight-electrode BIA model had also small, but systemic,

errors in fat percentage and fat-free mass. These errors led to an overestimation of fat percentage in lean individuals among men and an underestimation of fat percentage among obese women. Therefore, the general use of eight electrode BIA model should be interpreted with caution, until the valid or recommend equations or the correction of these total errors is resolved.

Caution is recommended when using BIA as the body composition method for breast cancer survivors who have completed treatment but are still undergoing adjuvant hormonal therapy [62]. The use of more than one method should be used to derive more physiologically reliable information, which could be potentially useful for providing validation to avoid such errors [67]. Lastly, the clinical benefit of BIA can be further enhanced by combining it with bioelectrical impedance vector analysis (BIVA) [69]. However there is a simple way of ensuring errors are reduced. By ensuring that candidates do their baseline reading at particular centre and ensuring that they repeat their testing at the same centre at the same time, many of the errors will be reduced. The difference between the two readings will be an accurate indicator of the changes in the subject's status

### Introduction to HRV

The origin of ECG is a special node which acts as a pacemaker for the heart. It is called the SA or Sinoatrial node, and assists in the acquisition of ECG when one attaches electrodes to specific points on the body, usually the right leg. The form and structure of the ECG as seen on a printed chart indicates whether an individual has a healthy heart or not. The first is the wave boundary and determination of the primary fiducial points, as shown by the onset and offset of the QRS complex as well as P and T waveforms. The baseline for the QRS-T is determined in an interval before the QRS onset. It is important to note that baseline wander, atrial fibrillation and a high or irregular heart rate can cause errors in ECG assessments.

Tests after tests show that the most suitable alternative for the development and assessment of ECG is the three channels CSE database, although it can only be used for assessments of one channel accuracy [70]. In order to accurately determine the ECG of an individual, several aspects are put into consideration. One of them is the HRV or Heart Rate Variability, which refers to the variation between the normal heart rate and a given mean value.

The autonomic nervous system innervates blood vessels, the airways, intestines and urogenital organs and is largely under involuntary control. It regulates and coordinates bodily functions by effecting secretory activity of glands and contraction and relaxation of smooth and cardiac muscle [71]. Autonomic neuropathy may be idiopathic or occur as a complication of other conditions or as result of drugs. It is recognised as a common complication in patients with diabetes mellitus; for many it remains subclinical, with only a minority experiencing symptoms such as postural hypotension, nausea, vomiting and early satiety related to gastroparesis, nocturnal diarrhea, bladder-emptying problems and male erectile dysfunction [72]. Autonomic

dysfunction (AD) has also been shown to be a negative prognostic indicator following acute myocardial infarction and stroke [73]. The underlying mechanism is thought to be an increased risk of cardiac arrhythmias as a result of decreased vagal tone [74]. Although the autonomic nervous system innervates all organs, due to the serious implications of cardiovascular autonomic dysfunction, investigation of autonomic function involving the cardiovascular system has become most established [75].

The heart rate may vary but may result from diabetes complications, fetal distress in a pregnant mother and congestive heart failure. One thing worth noting is that HRV is useful in predicting myocardial infarction. A reduced HRV is symptomatic of this condition which if left untreated is usually fatal. As said before, Heart Rate Variability is affected by Sympathetic and Parasympathetic system disorders, but those of the peripheral nervous and the central nervous systems also play a major role [76].

### Methods

**HRV analysis methods:** The first thing to note is that HRV methods for analysis of heart rhythms, do not generally involve opening up the body and physically examining the heart. Usually, doctors employ three different methods namely, the Non Linear, time domain, and frequency domain methods. Even with these methods, one ought to consider various factors such as the individual in question's health status, respiration, gender and age. Other parameters that generally influenced HRV tests were abnormalities in the Sympathetic nervous System (SNS) and Parasympathetic nervous system (PNS).

Short term power spectra analyses produce peaks or clusters of data points mostly within three main regions [72]:

A. High Frequency (HF) from 0.15Hz to 0.40Hz reflects the activity of the parasympathetic system and the vagal nerve.

B. Low Frequency (LF) from 0.04Hz to 0.15Hz reflects sympathetic activity.

Very Low Frequency (VLF) from 0.003Hz to 0.04Hz reflects a host of factors, including not only the sympathetic nervous system, but also input from chemoreceptors, thermoreceptors, the reninangiotens in system and others. According to most research journals, the most frequently used technique for HRV is the linear technique, specifically Spectral Analysis. In this method, spectral power in a high frequency band is employed to reflect respiratory sinus arrhythmias while at the same time, a low frequency reflects baro-receptors control. Very low frequency power on the other hand shows the vascular and thermo-regulatory functions of the heart [73].

### HRV analysis of diseases

Heart rate variation techniques and indexes have proved crucial in treating not just cardiovascular system diseases, but unrelated conditions such as stroke, Alzheimer, renal failure, leukemia, epilepsy, chronic migraines, and obstructive sleep apnea. Most doctors tend to agree that all biological systems,

even the healthy ones tend to show haphazard dynamics while biological systems suffering from disease show reduced levels of dynamics. Since all organs depend on the flow of blood from the heart, any cardiovascular abnormalities will affect all other organs and affect the heart rate activity.

That said, autonomic dysfunction is a key characteristic of heart and diseases such as sepsis, brain trauma, multiple organ failure, and myocardial infarction. Other conditions that show high HRV indices include Congestive Heart Block (CHB), Left Branch Bundle Block (LBBB), Sick Sinus Syndrome (SSS) and Premature Ventricular Contraction (PVC). As said before, Heart Rate Variability is affected by Sympathetic and Parasympathetic system disorders, but those of the peripheral nervous and the central nervous systems also play a major role [74,75].

### HRV analysis of cancer

Autonomic dysfunction has been described in patients with advanced cancer, in whom a high prevalence of AD is identified [68,76-79]. Postulated causes include decreased physical activity, treatment with vinca alkaloids or other medications, or paraneoplastic processes [80-87]. The precise contribution of AD to clinical findings and prognosis in advanced cancer is unclear. Only one study has demonstrated a relationship between AD and symptoms in patients with advanced cancer; Bruera et al. [80] found that patients with advanced breast cancer in whom all tests of cardiovascular autonomic function were abnormal were more likely to report symptoms of postural hypotension and chronic unexplained nausea [88-94]. More recent research on AD in advanced cancer has focused on its prognostic significance; a small number of studies have identified a relationship between AD and shorter survival in advanced cancer [95-100].

### Conclusion

ANS deregulation causes death from heart disease and HRV analysis, which provides information about the ANS in various ailments. ANS dysregulation is also observed in cancer. There appears to be a relationship between AD and survival rates in cancer. The small number of studies using the latter methodology means caution should be employed before any generalizations being made regarding the superiority of one technique over the other.

### Overall Summary

Both BIA and HRV provide a quick, low cost means to monitor the homeostatic reserves of a patient with cancer. They also provide means of assessing the efficacy of a treatment protocol as well as prognosis of survival rates. The author has used the above two assessment methods for the management of chronic conditions and cancer for almost fifteen years. The author has found these two approaches very complementary and useful in the prognosis and management of chronic conditions and cancer. By ensuring that candidates do their baseline reading at particular centre and ensuring that they repeat their testing at the same centre, many of the errors in BIA and HRV readings will be reduced. The difference between the two readings will be an accurate indicator of the changes in the subject's status. The small numbers of studies however suggest that further research should be undertaken before coming to any definitive conclusion.

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