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# The childhood maltreatment influences on breast cancer patients: A second wave hit model hypothesis for distinct biological and behavioral response

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ABSTRACT

Stress and cancer are two complex situations involving different biological and psychological mechanisms. Their relationship have long been studied, and there is evidence of the impact stress has on both, development and disease progression. Furthermore, early stress has been studied as an important factor associated to this relationship, since its impacts on the immune, endocrine and cognitive development throughout life is already known. Therefore, understanding early stress as a first wave of stress in life is necessary in order to explore a possible second wave hit model. From this perspective, we believe that breast cancer can be understood as a second wave of stress during development and that, in addition to the first wave, can cause important impacts on the response to cancer treatment, such as increased chances of disease progression and distinct behavioral responses. In this article we propose a second wave hit hypothesis applied to breast cancer and its implications on the immune, endocrine and cognitive systems, through mechanisms that involve the HPA axis and subsequent activations of stress responses.



## Introduction

### *The health burden of childhood maltreatment*

Childhood maltreatment is a complex social phenomenon that occurs as sexual, physical, or emotional abuse, as well as emotional or physical neglect [1]. Those environmental exposures are considered risk factors for the development of diseases, impairment during several life stages, and even death [2]. The "Global Burden Of Disease Studies", one of the biggest studies about the impact of diseases in the world, accounted 0,2 millions of death around the world because of sexual abuse, and 0,9% disability-adjusted life years (DALYS) [3]. Even though the study has not considered any other type of childhood maltreatment besides sexual abuse, it provides enough evidence to support that the extreme and prolonged exposure to stressors during the first years in the life can lead to long term deleterious effects on health [4–6].

Therefore, adults with a history of childhood abuse are at a greater risk of developing diseases than the ones who have not felt its impact. Among adults who have been exposed to any kind of childhood maltreatment, there is a high prevalence of health problems, such as cardiovascular diseases [7], diabetes [8], autoimmune diseases [9], cognitive deficits [10], chronic fatigue and cancer [11,12], and higher risk for premature death (about 20 years earlier than those without histories of maltreatment) [13], as well as telomere length reduction [14]. Those diseases can develop throughout a lifetime through the complex interactions between genes and the environment, which will be further discussed in the paper.

Among the risks for the development of diseases associated to childhood maltreatment, cancer has received little attention, noticeable by the few number of studies and the mixed results. Some studies show that negative childhood experiences are associated to higher risk of cancer development [15,16], while others shown no association at all [17,18]. A more recent study suggests that childhood maltreatment could be considerer a risk factor for the development of adult cancer before 50 years old (OR: 2.1) [19].

Another suggestion presented in the literature regarding maltreatment is about its role in the modification of many diseases clinical presentation. Some studies have shown that among

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individuals with the same diagnosis, those who have suffered from childhood maltreatment show a more severe clinical presentation of the disease, maybe leading to less successful treatment results [20]. Most of these studies focus on mental health issues and have explored the ecophenotype paradigm, which refers to when an environmental experience (such as childhood maltreatment) shapes a possible phenotypic alteration in a disease.

From this perspective, very few has been published regarding cancer, but some studies have found that breast cancer patients with a childhood maltreatment history show more psychosocial problems and a profile of biological reactions based on higher expression of inflammatory biomarkers, such as the Interleukin-6 (IL-6), a protein responsible for the immunologic system regulation. When its expression is prolonged, immunologic deficit risk during cancer treatment is increased [21–24]. Thus, this review aims at extending the relationship between childhood maltreatment as a first wave of severe stressors in the begging of an individual's life, and breast cancer acting as a second wave of severe stressors in this same individual's adult life, proposing a second wave hit model for breast cancer. The second wave hit model is derived from the diathesis stress model, which supports the idea that accumulated life stressors during a lifetime linearly increase the risk for health negative outcomes [25].

## The hypothesis: Second wave hit model for cancer and childhood maltreatment

Imagine yourself swimming inside an agitated sea. The moment a strong wave strikes, you need to spend even more energy to swim and survive. This would be the "first wave" that could be a metaphor for the first big life stressor, such as childhood maltreatment [26]. Surviving such severe exposure during such an early stage of life generates important costs to the endocrine, immune, and neurological systems, resulting in developmental impairments [27,28]. In this sense, the Hypothalamic-pituitary-adrenal axis (HPA) plays an important role in the attempts of regulating the hormonal and endocrinal means of dealing with the stress evoked from the severe exposure [29], possibly being overwhelmed, and therefore, generating an allostatic load [30].

When a second important life stressor takes place, the systems that were initially impaired tend to be even more fragile, resulting on insufficient psychological, endocrinal, and neurological responses to cope in an adaptive way with the second wave. As it has been said previously, the diathesis stress model considers that if there is a combination of individual proneness (such as genetics) and multiple stressors, the threshold for clinical manifestation of some disorders is progressively reduced [25]. The term diathesis is a synonymous of vulnerability. A vulnerability is what makes more likely that individuals will develop some pathologies if he, or she, has the genetics, or biological characteristics (diathesis) interacting with environmental influences (stressors) [31]. The second wave hit model would be a deployment of the diathesis stress model, but instead of gradual accumulation of lifetime stressors, it postulates that the first wave would sensitize the organism and a priming would occur that would program the organism to be more sensitive when faced with the strike of a second wave [32].

Therefore, knowing that exposure to childhood maltreatment for people with the same clinical diagnosis is associated with phenotypic differences in biological and clinical terms [20], we hypothesized that patients with breast cancer and a history of childhood maltreatment could manifest severe emotional symptoms (e.g. depression, anxiety) and a worse clinical prognosis (e.g. more side effects to treatment and increased mortality rates) when compared to patients without the history of that major stressor event.

## The first wave hit: The biological embedding of childhood maltreatment

Stressful situations occur during different periods in a lifetime, and generate emotional and physiological responses that mediate the choices of which strategies will be used to cope with the stressed environment [33]. Besides that, the first years of life are critical for the learning and acquisition of these strategies [34]. The child's brain is not fully developed, and when exposed to severe stressful situations, as childhood maltreatment, it can be programed in a way that will process all future life stressors [35].

In this regard, physiological responses to stressful events involve the central nervous system (CNS), central perceptions of threats and the subsequent activation of the autonomic nervous system (ANS), as well as the HPA-axis [36]. Consequently, going through an early life stress can cause damage to all these systems. However, the mechanisms through which these associations occur are not well described yet, even though it is already recognized that a chronic activation of the HPA axis could have long-term negative effects on brain development and other biological systems such as immune, cellular and neurotrophic pathways [37,38].

Cortisol excessive production can have negative effects on general health, because cortisol helps inhibiting the HPA-axis activity through a feedback system [39] that is responsible for allowing the system's activation to return to baseline after a stressor event is over. Cortisol regulation is mediated by the Glucocorticoids (GRs) receptors located at many cerebral areas, mainly at the hippocampus, hypothalamus and pituitary, leading to the suppression of the CRH (Corticotropin-releasing hormone), ACTH (adrenocorticotrophic hormone) and glucocorticoids [40]. This regulation has the role of producing adaptive responses to social and psychological stressors, preparing the organisms to anticipate and respond efficiently when faced with a threat, and to return to a homeostatic balance when the ceases [41].

Therefore, the activation of the HPA-axis as a response to early stressors, such as childhood maltreatment, can lead to impacts on cerebral areas responsible for emotional processing [34]. This impact can cause daily stressful situations to be interpreted as threats, thus hyperactivating the axis [42], while it should be hyporesponsive, harming executive functions and memory [35].

Besides all of it, childhood maltreatment history is regarded as a risk factor for many psychological disorders, such as depression [43], bipolar [44], psychosis [45] and substance abuse [20]. In terms of physical health, adults with a history of childhood maltreatment are at higher risk of developing some other diseases, such as cardiovascular disease [7], diabetes [8], autoimmune diseases [9], cognitive deficits [10], chronic fatigue and cancer [11,12,46].

Those diseases can be developed during the lifetime through complex interactions between genes and environment [20]. There are some evidences regarding aging and early stress during a period of higher neurobiological sensitivity [37]. As a matter of fact, there is a large scope of researches that focuses on neurobiological aspects of early stress and early aging, proposing some mechanisms of actions, including the shortening of telomeres [11,30,47].

The shortening of the telomeres occur every replication DNA cycle, and can be interpreted as a biological aging biomarker [11]. The size of the telomeres is influenced by stress and by inflammatory factors, and some studies have already shown that severe chronic diseases involve stressful and inflammatory states that can contribute to the association of the telomeres' size and physical diseases [38], such as cancer. This relationship can happen, mainly, because of the fact that the telomeres are specialized structures that protect the extreme of the chromosomes, and participate in many relevant processes at cellular level, making it