

Review article

Does obesity during childhood/adolescence modify the risk of developing cancer in Previvors?

6

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Introduction

Obesity is a chronic multifactorial disease characterized by the excessive accumulation of body fat. It increases the risk of other chronic metabolic diseases (e.g., metabolic syndrome, diabetes, cardiovascular diseases, and infertility) and cancer. The global prevalence of obesity is estimated to be 22.4%, and Mexico has one of the highest rates compared to other countries [1]. Obesity begins to manifest during childhood/adolescence and quickly progresses to a chronic health condition. It begins when an individual becomes overweight and notices that various body areas increase in volume due to adiposity. Although this condition is multifactorial, it is due to being unable or unaware of how to balance caloric intake and energy expenditure. In other words, obesity develops when an individual consumes more calories than they expend each day. Hypercaloric diets are associated with consuming ultra-processed foods, typically produced by commercial companies. Food intake behaviors are reflected in the habits, activities, and customs associated with the social, cultural, and economic environments in which an individual exists. Parents, family, or friends help create and reinforce these intake behaviors. Many of these behaviors are enhanced by anxiety situations, reflected in the desire to try greasy, crunchy, or strongly flavored foods. Various mental health disorders, primarily associated with personal circumstances (e.g., anxiety, fear, and depression), result in changes to daily routines and practices, such as increasingly sedentary lifestyles. However, the lack of orientation towards the transition into adulthood and the illnesses associated with this is of greatest importance. Social

anthropology contributes to the field of medicine with the concept of syndemics, which suggests that diseases are not isolated entities but are interconnected and influence each other in social and cultural contexts [2].

Excess body fat has been linked to the increased prevalence of many types of cancer, which typically manifest in adulthood. However, it is becoming increasingly common for cancer to be detected and diagnosed in younger individuals (< 40 years of age) [3]. Although there are limited studies linking early-age obesity and cancer, it is estimated that between 4-8% of cancers could be attributed to obesity. Therefore, obesity is a risk factor associated with the development of different types of cancer that have high prevalence and mortality rates, including postmenopausal breast, colorectal, endometrial, kidney, oesophageal, pancreas, liver, and gallbladder cancer. Evidence suggests that excess body fat increases the risk of cancer-specific mortality by approximately 17%. The relationship between obesity and cancer development and recurrence is not yet fully understood; however, it is thought to involve alterations in the cellular metabolism of fatty acids, remodelling of the extracellular matrix, adipokines and anabolic and sexual hormone secretion, immune dysregulation, and chronic inflammation [4]. There is no clarity regarding the relationship between obesity and the increased risk of cancer associated with Previvors. "Previvors" refers to a group of people, almost always direct relatives of individuals with cancer, who are carriers of a pathogenic variant that predisposes them to developing cancer

457

[5]. The term was coined by the non-profit organization Facing Our Risk of Cancer Empowered (FORCE) to create an identity and meet the needs of these individuals who face difficulties due to receiving positive genetic diagnoses indicating a predisposition to cancer [6]. It has been proposed that these individuals should receive legal support as they should receive routine and periodic medical monitoring and treatment throughout their lives [7]. Initially, the term was proposed to describe women carriers of the BRCA1 and BRCA2 genes, which are associated with an increased risk of Hereditary Breast and Ovarian Cancer Syndrome. However, it has been demonstrated that this syndrome is also associated with other genes, such as PALB2, CDH1, NF1, PTEN, TP53, STK11, and BARD1. Furthermore, men are also at risk of developing this condition, as in addition to the breasts and ovaries, cancer may develop in the pancreas, skin, endometrium, and prostate [8].

The risk of Previvors developing cancer is not fixed and increases based on age, lifestyle, and the specific genetic variant of the affected gene [9]. Depending on their homozygosity or heterozygosity, some pathogenic variants exhibit variable expressivity and behave differently within a family, impacting whether penetrance is complete or incomplete. This means some Previvors will develop cancer while others will not [10]. The mechanisms driving this are unknown, as are the factors that may lead to one Previvor developing cancer and another not. However, this could be related to lifestyle (e.g., excess caloric intake) and exposure to environmental carcinogens (e.g., tobacco smoke, particles > $10\mu m$), as well as factors that alter the DNA structure or epigenetics of an individual. Considering obesity as a risk factor for developing cancer in already high-risk people, we propose that Previvors should avoid weight gain and obesity to reduce their risk of developing cancer and avoid the adverse effects associated with decreased risk treatments [11]. Furthermore, this parameter should be considered when making decisions about follow-ups and riskreducing treatments (e.g., chemopreventive and surgical) [5]. This assumes that the benefits observed with long-term sustained weight loss and moderate physical activity could be a strategy for cancer

prevention in the general population and particularly in Previvors, as well as enabling a better quality of life for cancer survivors. The development of constant and highly structured exercise routines in combination with dietary support and ad hoc behavioural therapy for this population could become an effective intervention that prevents or delays the presentation of hereditary cancer syndromes [3]. In conclusion, obesity is largely the product of an obesogenic culture generated by the commercial industry and socioeconomic, cultural, and familial factors that promote sedentary lifestyles. This, combined with low dissemination of information, little or no food education, gaps in dietetics that need to be visualized, and deficits in the continuity of care for obesity, exacerbates the problem. Further studies on Previvors are needed to determine why only some develop neoplastic disease to determine whether obesity is a risk factor and if implementing consistent and specific exercise routines and improving dietary education could reduce the need for surgical and prophylactic chemo preventive approaches and mitigate the associated psycho-emotional consequences. Such actions could be implemented in early childhood, when obesity begins to manifest in many regions, including Latin America. Such actions could improve Previvors' quality of life, delay or prevent disease onset, and improve biopsychosocial stability. Figure 1. People who have Genetic/Familial High-Risk for cancer. A Survivor of cancer is an individual with a history of malignancy, who has lived through a personalized challenge and has ongoing positive and negative consequences. In this context, not only is a survivor but also carries an inherited Pathogenic/Likely Pathogenic Variant PV/LPV cancer risk to relatives. A previvor is a person who carries an inherited (PV/LPV) in a known cancer-predisposing gene to relatives. 1) Accumulation and excess fat result in adipose tissue dysfunction, which contributes to tumor initiation, growth, and recurrence. 2) Overweight and obesity promote the development of neoplastic disease and worsen its effects. 3) Structured exercise routines combined with dietary support and behavioral therapy in Survivors and Previvors could improve the quality of life, delay the onset of the disease, and contribute to mitigating the psychological effects resulting from genetic diagnosis and risk-reducing surgeries.





List of Abbreviation:

Facing Our Risk of Cancer Empowered: FORCE.

Pathogenic/Likely Pathogenic Variant: PV/LPV.

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