SYMPOSIUM OBESITY AND REPRODUCTIVE HEALTH

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Obesity and gynecological cancer
Obesidad y cáncer ginecológico

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ABSTRACT
Obesity is a growing public health problem and its association with some chronic diseases, including some types of cancer, mainly breast cancer and endometrial cancer, is increasingly clear. In this review we analyze some mechanisms of this relationship, such as: aromatization in fatty tissue, insulin resistance, chronic inflammation and immune dysfunction.
Keywords: Neoplasms, Obesity, Breast neoplasms, Endometrial neoplasms, Ovarian neoplasms (source: MeSH NLM).

RESUMEN
La obesidad es un problema de salud pública creciente y es cada vez más clara su asociación con algunas enfermedades crónicas que incluyen algunos tipos de cáncer, principalmente el cáncer de mama y cáncer de endometrio. En esta revisión analizamos algunos mecanismos de esta relación como son: la aromatización en el tejido graso, la resistencia a la insulina, la inflamación crónica y la disfunción inmunológica.
Palabras clave: Cáncer, Obesidad, Cáncer de mama, Cáncer endometrial, Cáncer de ovario (fuente: DeCS BIREME).

Introducción

Obesity is related to several diseases, in fact, it is already a health problem in many countries and cancer is not alien to it, specifically gynecological cancer[(1)]. Some cancers are closely related to obesity in their etiopathogenesis, by a hormonal mechanism, by chronic inflammation, by immunological dysfunction or perhaps by insulin resistance. Regarding the hormonal aspect, obesity increases estrogen levels favoring the carcinogenesis of hormone-dependent cancers, aromatization is a phenomenon that occurs in peripheral fatty tissue converting androgens such as androstenedione and testosterone into estrogens. Chronic inflammation releases prostaglandins and proinflammatory cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α), which favor tumor growth. Immune dysfunction can alter the mechanisms of cellular apoptosis. Finally, insulin resistance leads to elevated levels of insulin and insulin-like growth factor (IGF-1) that stimulate cell proliferation.

The cancers most associated with obesity are: breast cancer (postmenopausal), endometrial cancer, colon cancer, kidney cancer, liver cancer, pancreatic cancer, rectal cancer, esophageal cancer, and ovarian cancer[(2)]. Furthermore, the prognosis of response to treatment and the percentage of disease recurrence are also related to the presence or absence of obesity, constituting, among others, a factor of poor prognosis in many neoplasias[(3)].

Obesity and breast cancer

The risk of developing breast cancer increases as the population ages, as can be clearly seen in the increase in the average survival age of the population. Likewise, lifestyle is closely related to the increased risk of breast cancer. Among the risk factors for breast cancer are obesity, specifically in menopausal women, early menarche, late menopause, nulliparity, first birth after age 30, higher rate of abortions, prolonged use of oral contraceptives, hormone replacement therapy, especially without

progestogen opposition. Obesity is an important risk factor in the predisposition to develop breast cancer compared to the normal weight population in menopause, and this factor is controversial in premenopause. Although the ovaries stop producing estrogens in menopause, in obese patients peripheral fatty tissue becomes an important source of aromatization due to the increase in this tissue. The conversion of androgens into estrogens is a process that occurs by aromatization that comprises three steps, hydroxylation, oxidation and demethylation that occurs in the C19 ring converting it into a C18 phenolic ring, this occurs to maintain hormonal balance. The aromatase that is responsible for this conversion is found in various tissues such as adrenal glands, brain, liver, breasts, ovaries, Leydig cells of the testicles, muscles, bones and fatty tissue. With the increase in fatty tissue, aromatization increases and therefore estrogen levels are high, something that should no longer occur in menopause. Estrogens stimulate the growth of breast cells and therefore the risk of breast cancer increases.

On the other hand, breast cancer is usually diagnosed in more advanced stages in obese women with a lower response to treatment and lower survival[4].

Endometrial cancer

Endometrioid endometrial cancer (EEC) is a model of a direct relationship between obesity and cancer[5]. It is the second most common neoplasia related to obesity after breast cancer. Endometrial cancer is a health problem in high-income countries and is also becoming an increasingly common pathology as the rate of obesity and aging of the general population increases. The risk of endometrial cancer associated with obesity, low physical activity and inadequate diet increases this risk by up to 80%[6].

EEC corresponds to the already classic type 1 endometrial cancer described by Bokhman, it is basically linked to the estrogenic load without progestogenic opposition and is usually a well or moderately differentiated tumor, it has on a very good prognosis of over 90% of overall survival. This is characteristic of women with obesity, polycystic ovary syndrome, nulliparity, early menarche, late menopause and hormone replacement therapy, especially without progestogen opposition. It is associated with mutations in different genes (molecular classification), the most common of this group being PTEN, and also others such as PIK3CA, K-ras, CTNNB1 (β-catenin), PIK3, ARID1A and microsatellite instability (MLH1, MSH2, MSH6, PMS2). On the other hand, type II endometrial cancer is much less frequent and has a worse prognosis. It is not related to estrogenic aggression or obesity (normal weight). They are high-grade tumors and are frequently associated with mutations in TP53 (90% of serous carcinomas), p16, CDH1 (E-cadherin), ERBB2 (HER2/neu) among others[7,8]. To date, it is of utmost importance to refer to the genetic mutations that have allowed a molecular classification to define the best systemic treatment (chemotherapy or immunotherapy) or regional when necessary, in this way molecular tests are part of the current management and prognosis of this disease; in this, four groups are distinguished: POLE, microsatellite instability (deficiency in the repair of disorders), abnormal p53 and without specific molecular profile[9]. Even the molecular study allows to reclassify the histological diagnosis in some difficult cases during the anatomopathological study[10].

Obesity plays an important role in the etiology of CEE through several mechanisms. The estrogenic hormonal mechanisms of androgen aromatization in peripheral fat already mentioned allow the release of estrogens without progestogen opposition during menopause, and the decrease in the sex hormone binding glycoprotein (SHGB) produced in the liver is also relevant, which allows a greater proportion of free active hormones, leading to chronically high levels of estrogens with hormonal activity. On the other hand, the association with insulin resistance stimulates the production of estrogens with the consequent increase in estrogen receptors in the endometrium and the activation of the insulin-like growth factor and its receptor (IGF-1 and IGF-1R), promoting the development of endometrial cancer. It is possible that low levels of 17OH-progesterone and 11-deoxycortisol determine greater tumor aggressiveness, while high levels of androstenedione are associated with a higher risk of endometrial cancer. Finally, the process of chronic inflammation plays a role in many human diseases, including some types of cancer such as EEC. Although insulin resistance,

metabolic syndrome and inflammation increase the risk of endometrial cancer, the prominent role of chronic inflammation has been pointed out as being of utmost importance. This occurs in the stroma and not in the adipocyte, where cellular hypoxia is very likely to aggravate this process[11,12].

Ovarian cancer

Ovarian cancer has also been linked, but only distantly, to obesity, and is far from the relationship seen with breast cancer and endometrial cancer. Some studies suggest that their relationship may even be linked to obesity from an early age[13,14]. This weak relationship between obesity and ovarian cancer has even been documented by meta-analysis, with a positive relationship being observed in premenopause but not in postmenopause. In addition, this relationship has been linked to mucinous and clear cell histological types but without a relationship with serous and endometrioid types[15].

A recent review shows a protective benefit against ovarian cancer with the use of aspirin. The mechanisms linking the relationship of these factors with ovarian cancer are still a matter of further study[16].

Measures for early diagnosis

Consequently, obesity is considered a contributing factor to the increased incidence of gynecological malignancies such as breast, endometrial and ovarian cancer[17]. Prevention of these neoplasms is based on primary and secondary strategies; for breast cancer, early detection by mammography and breast ultrasound is essential in women from 40-50 years of age, depending on individual risk. In addition to this strategy, modifiable factors such as maintaining a healthy weight, engaging in regular physical activity and reducing alcohol consumption are also important[18]. On the other hand, women with BRCA1/2 mutations constitute a high-risk population, in whom monthly breast self-examination, biannual clinical examination and annual mammograms should be included from the age of 25-35 years. In some of these women, prophylactic mastectomy and the use of selective estrogen receptor modulators, such as tamoxifen, are recommended[19].

In the case of endometrial cancer, overweight and obesity, as well as the prolonged use of unopposed estrogen, are closely related risk factors. As these are modifiable factors, prevention of this neoplasm includes weight control and the appropriate use of hormonal contraceptives in the treatment of conditions such as polycystic ovary syndrome and contraception itself[20]. This neoplasm mainly affects post-menopausal women, it is essential to warn them of the importance of seeking early medical attention if they experience vaginal bleeding. On the other hand, ovarian cancer is the most lethal gynecological neoplasm due to its mostly asymptomatic development. Early detection is made difficult by the lack of a specific symptom pattern and screening tests applicable to the general population. However, it is recommended that the annual gynecologic examination include a transvaginal ultrasound, especially in women with a family history of the disease[21].

Finally, there are many challenges to mitigate the impact of obesity on health; Healthy lifestyles, healthy eating, regular physical activity, and medical and surgical interventions are an increasingly popular alternative should be promoted. These strategies should be combined and adapted to reduce the prevalence of obesity and thus decrease the risk of cancer.

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