Mini Review

Could metabolic risk factors contribute to the development of cervical cancer?

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Abstract

The role of human papillomavirus infection as etiological factor for cervical squamous intraepithelial lesions and cervical cancer is well established. However, the presence of this virus is not sufficient condition for developing of cervical cancer. Currently, the contribution of other viral, environmental and host cofactors in triggering of this neoplasm is being investigated. Some metabolic risk factors have been associated with the development of several gynecological cancers such as endometrium, ovary and cervix. However, the mechanisms through which these factors contribute to carcinogenesis are complex and not fully elucidated. Few interventions regarding host metabolic factors have been performed on women at risk of developing cervical cancer. Some specific treatments and or changes in lifestyles could be carried out to avoid or delay progression to this kind of cancer. This paper aims to enlarge and update this topic based on the article ¨Association between components of the metabolic syndrome and degree of cervical squamous intraepithelial lesions in Cuban women¨, with emphasis on possible mechanisms that explain the link between central adiposity, insulin resistance and dyslipidemia with risk of premalignant lesions and cervical cancer.

Introduction

Although cervical cancer (CxCa) is considered a largely preventable and potentially curable disease, it is among the neoplasms with the highest incidence and mortality in females. In 2017, 601,000 new cases were detected worldwide, and 260,000 deaths occurred by this cause. However, the majority of deaths took place in low and middle-income countries [1]. In Cuba, 1438 new cases of CxCa were diagnosed, with a rate of 25.5 per 100,000 inhabitants, so it is ranked fourth in incidence among tumors affecting the female sex (2015). In addition, 548 deaths occurred, with a rate of 9.7 per 100,000 inhabitants, which places it in fifth place in mortality (2018) [2]. In Cuba, there is a Program for Early Diagnosis of Cervical Cancer [3], through which all women from 25 years are tested by cytology every three-years. For economic reasons the current program does not include prophylactic vaccine or HPV molecular test-based screening. World Health Organization (WHO) has recommended HPV vaccines because of its effectiveness as primary prevention tool. It is supposed vaccination could reduce CxCa and other cancers associated with this infection [4]. Despite the potent effect of the vaccine, it is only applied in adolescents of both sexes from 9 to 13 years, prior to the beginning of sexual intercourse, and its impact on the reduction of these neoplasms could be confirmed in a few decades. Currently, there are a large number of women who have already acquired the infection, or are at risk of acquiring it, who will not benefit from immunization and require efficient secondary prevention policies to avoid the development of CxCa. These strategies include screening, detection and control programs, which allow the early diagnosis of HPV by molecular tests, detection of lesions by cytological, colposcopic and histological studies, as well as the elimination of them by excision or ablation [5]. Screening programs differ between different countries. The most frequent method is cytology, but HPV DNA detection is being introduced in many countries alongside cytology ("co-testing") or for primary screening, followed by cytology [6,7].

Some studies about HPV prevalence have carried out in selected populations of Cuban women. These researches reported HPV frequency of 66% - 76%, with higher records in women with premalignant lesions (91% - 94%). The risk factors for the acquisition of the infection found were the low educational level, beginning of sexual intercourse before the age of 15, menarche from 10 to 14 years, consumption of cigarettes and alcohol, menopausal stage and use of oral contraceptives. Additionally, there was a predominance of high-grade lesions in women under 20 years. These results show a high prevalence of HPV infection among the studied women and justify the introduction of vaccination and HPV molecular tests in the near future [8,9]. Although persistent HPV infection is the main etiological factor for the development of CxCa, other viral, environmental and host cofactors participate in cervical carcinogenesis [10]. The interaction between the virus and the host is of vital significance, since it will depend on the clearance or persistence of the infection. Host-related factors include immunological response, nutritional status, genetic and epigenetic factors, as well as metabolic risk factors, which influence has been investigated in latest years [11]. Based on the recently published article about the association of some metabolic syndrome components with the degree of precursor lesions of CxCa [12], this work aims to enlarge and update this topic with emphasis on possible mechanisms that explain the link between central adiposity, insulin resistance and dyslipidemia with risk of premalignant lesions and CxCa.

Influence of abdominal obesity on CxCa risk

As is known, there is a high global prevalence of overweight and obesity [13]. Health risks related to obesity include type 2 diabetes mellitus (DM2), hypertension, cardiovascular disease and some types of cancer. However, for the female sex there are additional risks such as polycystic ovary syndrome, anovulation and infertility. In the same way, excess weight, which has a stimulatory effect on carcinogenesis, is associated with a higher incidence of some gynecological cancers such as endometrial, ovarian and cervical cancers [14-17]. Some mechanisms have been proposed supporting obesity contribution to risk and progression of cancer. Because of calories excess ingestion, occur some processes like adipose tissue enlargement (hyperplasia and hypertrophy), immune cells infiltration and extracellular matrix remodeling of adipose tissue [18]. Adipocytes and stromal cells from white adipose tissue, cooperatively, modulate important signal pathways involved in initiation and progression of cancer. These include glucose intake, cell growth, proliferation and angiogenesis, which increase the risk of oncogenic transformation [16,19]. Additionally, abdominal obesity specifically is related to chronic subclinical inflammation, hyperinsulinemia, as well as changes in the circulating levels of steroid hormones, glucose and lipids. It is also linked to variations in the levels of proinflammatory cytokines (IL-6 and TNF α), adipokines (leptin, adiponectin) and insulin-like growth factor 1 (IGF1) [20].

In this study a significant association between abdominal obesity, expressed as waist circumference, WHR and WHtR, and presence of high-grade cervical squamous intraepithelial lesions (HSIL) was found [12]. However, BMI was not associated with HSIL. Obesity definition based on BMI has recently been questioned [21], since the anthropometric phenotype does not always reflect the state of health. It has been shown that BMI is inadequate to identify individuals with adipose tissue inflammation. Chronic low-grade inflammation state has been observed in a group of individuals with normal BMI, while a minority of individuals with elevated BMI is metabolically healthy [22]. Based on these results, waist circumference could be more useful in defining the relationship between obesity and premalignant lesions and CxCa.

In many countries, obesity is one of the most important health problems, related to lifestyles [14]. Among risk factors associated with cancer, this is one of the few that can be modified. In Cuba, there has been an increase in overweight, obesity (both general and abdominal) and sedentary lifestyle, with predominance in feminine sex [23]. Because of CxCa is a slow evolution disease, preceded by premalignant lesions whose progression occurs over several years, there is an excellent opportunity to carry out interventions at the level of primary health care. Because of obesity contribution to this neoplasm, it could be possible to identify patients at risk of CxCa with overweight or obesity. It is possible to carry out by algorithms recommended for obesity management in family medicine, pediatrics and gynecology and obstetrics [24]. In this way, subgroups of women with a higher risk of CxCa could be counseled about diet modification, physical activity increase, pharmacological therapy, bariatric surgery and psychological support [25-28].

Contribution of Insulin resistance to CxCa risk

Regarding to impaired glucose metabolism (IGM), its presence was significantly associated with HSIL [12]. Insulin resistance was the most important component in this association. There are some reports about possible connection of insulin resistance with the development and progression of various types of cancer, although the relationship with CxCa is controversial [29]. Insulin resistance could increase cancer risk directly through the mitogenic effect of this hormone and indirectly by increasing IGF1, which is produced in the liver by the action of growth hormone (GH) [30]. Therefore, chronic hyperinsulinemia is associated with high concentrations of circulating IGF1, not only because of the stimulation of its production but also because the suppression of insulin-like growth factor binding proteins (IGFBP), which serve to limit the bioavailability of IGF1 in peripheral tissues [31]. IGFBP3 is the most abundant and has protective and antiapoptotic effects, which can be exercised independently of IGF1 [32]. The binding of IGF1 to its receptor (IGF1R), and others related to IGF system, triggers a series of events that result in the recruitment and activation of second messengers like

phosphatidylinositol 3-kinase/protein kinase B signaling (PI3K/AKT) pathways and the mitogen-activated protein kinase (MAPK) pathway. The PI3K/AKT pathway has various effects such as regulation of metabolic processes, activation of antiapoptotic pathways and stimulation of protein synthesis, while MAPK pathway has mitogenic effects such as cell growth and proliferation. IGF1R is expressed in almost all body tissues and activates multiple signaling pathways, which net result is promotion of cell proliferation and differentiation and apoptosis blocking [33].

Many studies have found elevated levels of IGF1 and 2 in the blood of patients with SIL and CxCa [34], as well as IGFBP3 [35], although these results have not confirmed in all the investigations carried out [36,37]. It has suggested that the axis of the IGF is a pro-carcinogenic pathway, together with the epidermal growth factor receptor (EGFR) pathway, used by HPV during cell replication and transformation. Viral oncogenic proteins E6 and E7, in addition to modulate IGF1R expression, can bind to IGFBP 2, 3 and 5. This increases IGF availability and the possibility of binding to its receptors, which is a key element in cervical carcinogenesis. In addition, E7 interacts directly with IGFBP3 and inhibits apoptosis mediated by this protein [38]. It has also shown that in 85% of women with HSIL, IGFBP 2 loss expression occurs, which could has clinical utility for monitoring patients with a higher risk of CxCa progression [39]. Some epigenetic mechanisms have been described in CxCa, related to the effects of HPV on viral and host genome [40,41]. Some of them involve the components of the IGF system, such as IGF2 loss of imprinting, which can lead to some genes overexpression and overall chromatin instability [42] and E7 interaction with a group of lncRNA that modulate PI3K/Akt/mTOR and Wnt-β catenin pathways in cervical carcinogenesis process [43]. It is expected that epigenetic factors that are induced by HPV or triggered in response to viral infection/viral protein expression could be important drug targets for viral associated cancers [39]. The reversibility of epigenetic modifications makes such factors ideal therapeutic targets. Several drugs targeting chromatin modifiers are already in use in the clinic [44].

A group of target-directed therapies has been tested against the pathways that involve IGFR and EGFR, with limited clinical impacts due to the development of resistance mechanisms. However, the combined inhibition of these molecular targets has given better results [45]. On the other hand, it have been demonstrated that metformin, a drug commonly used in DM2 treatment, significantly reduces the risk of CxCa when it is used for more than two years [46]. It could be a cost-effective treatment for those women at risk of CxCa with insulin resistance.

Implications of dyslipidemia in CxCa risk

Circulating lipid concentrations have been consistently associated with cardiovascular disease (CVD), however, their relationship to cancer risk are contradictory. Dyslipidemia, defined as lipid and lipoprotein modified concentrations in blood, was significantly associated with the presence of HSIL [12], which are the immediate precursors of CxCa. This result is consistent with a meta-analysis that took into account 28 epidemiological studies. It concluded that high blood concentrations of triglycerides (TG) and low concentrations of high-density lipoprotein (HDL-c) were associated with the increased risk of overall incidence of cancer [47,48]. Similar results were found in another study focused on some neoplasms affecting the female sex [49].

It is difficult to define a common lipid profile for cancer risk, due to inconsistency of a few studies carried out [50]. In 2012, Ulmer, et al. found a relationship between the high concentration of TG and obesity with the risk of developing CxCa [51]. Similarly, the high risk of recurrence in patients with early stages of CxCa has been related to hypertriglyceridemia [52]. High levels of TG are linked to development of oxidative stress and generation of reactive oxygen species (ROS), which are increased in cancer [53]. ROS could cause double stranded DNA breaks and a reduction in DNA repair capacity of the cell [54].

A carcinogenic role is attributed to TG because they are an independent source of fatty acid oxidation, which is an important process in the promotion of cell proliferation [55]. Fatty acid metabolism is linked to the cancer-obesity relationship, due to excess lipid accumulation, particularly, in abdominal regions [56]. Lipoprotein lipase (LPL) is found in the cell membranes of adipocytes, whose function is to hydrolyze TG from lipoprotein to facilitate its entry into the cell. It has observed an overexpression of this enzyme in some types of cancer. This is related to an increase in the invasive capacity of the tumor, due to a polymorphism of this molecule (Ser447 stop) [57]. At the same time, two homologous isoforms of the enzyme 1-acylglycerol-3-phosphate-O-acyltransferase (AGPAT), which is part of the fatty acids activation pathway, have been found overexpressed in breast cancer and CxCa. This overexpression enhances the esterification of fatty acids and the subsequent accumulation of these in the lipid gout, which represents the main cause of abdominal obesity [58].

Previous studies have shown that HDL-c, which plays an important role in the reverse transport of cholesterol, has a protective effect against the development of tumors. It has an influence on signaling pathways, by modulating the cholesterol content in cell membranes, its antioxidant and anti-inflammatory properties. Aditionally, HDLc play a role in inhibiting the oxidation cascade of low-density lipoprotein (LDL), which contributes significantly to ROS generation. Another mechanism that involves apo (a), the main HDLc protein, is the inhibition of cell proliferation and cell cycle progression [59-61]. Decreasing HDLc concentration and lipid composition changes have been observed in overweight or obese individuals, insulin resistance, DM2 and CVD [62,63]. Alterations in enzymes and proteins that make up the HDLc

particles result in changes in their activity, in conditions of oxidative stress, infection and inflammation [64].

Low HDL-c blood levels is a mechanism that shows the relationship between abdominal obesity-dyslipidemia-cancer. Inflammation leads to a series of changes in lipid metabolism, whose main objective is to reduce the toxicity of various agents that it generates and repair the damage caused by it. Once it becomes a chronic low-grade condition, the inflammatory cascade is activated, which induces a decrease in the plasma concentration of HDL-c in the blood and a subsequent increase in the blood concentration of TG. When this compensatory response is not able to repair the damage, it becomes harmful and the change in the lipid profile becomes chronic [65]. Intervention strategies to reduce TG and increase HDL-c, used in the prevention of cardiovascular diseases, could have beneficial effects in the prevention of cancer [47,66]. This preventive action could be implemented in women at risk of CxCa with dyslipidemia.

Conclusion

Metabolic risk factors such as abdominal obesity, insulin resistance and dyslipidemia could be related to the development of premalignant lesions and CxCa. Taking into account this neoplasm is a slow evolution disease, during the time between low-grade lesions appearance and CxCa beginning, additional interventions could be performed to those established in the prevention and control programs. Some of them could be modifications in host metabolic risk factors, through cost-effective actions such as variations in diet, physical activity increase and pharmacological treatments. This strategy could have satisfactory results in preventing or delaying CxCa development.

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