State of the art paper

Correlation between gynecological tumors and atherosclerotic diseases

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Abstract

Gynecological cancer is among the leading causes of cancer-related mortality worldwide, with malignancies of the ovary, uterus, fallopian tube, cervix, vagina, and vulva making up 10–18% of all cancers diagnosed in women globally. Gynecological cancer and atherosclerosis are two of the most frequent medical entities that afflict women worldwide; thus the possible correlations between them ought to be explored. Vulvar, cervical, vaginal, endometrial, and ovarian cancers have been found to have common points with atherosclerosis regarding their pathogenesis and predisposing factors. Obesity and metabolic syndrome, HPV infection, vitamin D deficiency, and increased telomere length constitute common ground between these two afflictions, which this article aims to analyze.

Key words: atherosclerotic diseases, vulvar cancer, gynecological tumors, vaginal cancer, cervical cancer, endometrial cancer, ovarian cancer.

Introduction

Atherosclerosis is the primary cause of vascular disease globally, being responsible for approximately 30% of all deaths worldwide with 9.6 million men and 8.9 million women dying due to cardiovascular disease [1]. Gynecological cancer at the same time is amongst the leading causes of cancer-related mortality worldwide, with malignancies of the ovary, uterus, fallopian tube, cervix, vagina, and vulva making up 10–18% of all cancers diagnosed in women globally [2]. The aim of this article is to examine the possible correlations that exist between these two entities by exploring the currently available literature.

Vulvar cancer and atherosclerosis

Vulvar cancer is an uncommon gynecological malignancy representing approximately 5–6% of all female genital tract malignancies and primarily

affecting postmenopausal women. Vulvar cancer most frequently occurs in women 65 to 75 years of age. The mean age of incidence has fallen in recent years owing to the increase in human papillomavirus (HPV) infections worldwide [3]. There will be an estimated 6190 new cases of vulvar cancer in 2018, accounting for 0.4% of all cancers. This is primarily a disease of the elderly with a median age at diagnosis of 68 years. The incidence of vulvar cancer has been increasing by an average of 0.6% per year [4].

Recent evidence suggests that vulvar cancer is composed of two separate diseases. The first type may develop from vulvar intraepithelial neoplasia caused by human papillomavirus infection and is increasing in prevalence among young women. The second type, which more often afflicts older women, may develop from vulvar non-neoplastic epithelial disorders (VNED) as a result of chronic inflammation [5]. Age, first coital age, educational level, smoking, atrophic vagina history, HPV infection, lesion sites of the upper vulva, and histopathological changes are the risk factors that lead to vulvar cancer [6]. Hypertension, diabetes mellitus, and obesity have been found to coexist in up to 25% of patients, although they are not considered independent risk factors [7]. A retrospective review of women with vulvar cancer found a statistically significant correlation between patients younger than 45 years and HPV (relative risk (RR), 11.34), cigarette smoking (RR = 2.83), having more than two sexual partners (RR = 2.87), sexual initiation before age 19 years (RR = 2.43), and low economic status (RR = 1.77). In patients older than 45 years, there was a statistically significant correlation between VIN and vulvar cancer and VNED (RR = 23.6), residence in a rural area (RR = 2.17), low economic status (RR = 1.89), menopause before age 45 (RR = 1.84), poor hygiene (RR = 1.76), endocrine disorders (RR = 1.94), and low serum vitamin A levels (RR = 1.78) [8]. Human telomerase reverse transcriptase is upregulated in vulvar neoplasia, which contributes to cellular longevity and resistance to apoptosis as associated features, independent of the etiology of vulvar intraepithelial neoplasia [9].

Finally, in the prospective population-based Bruneck study, baseline telomere length was a significant risk predictor for subsequent myocardial infarction and stroke, independent of standard risk factors. Of note in this study was that telomere length was strongly associated with advanced pathology and acute vascular syndromes but not early atherosclerosis [10].

Vaginal cancer and atherosclerosis

Vaginal cancer is a rare gynecologic malignancy representing only 1–2% of all gynecologic neoplasms [11]. The reported incidence rate of vaginal cancer is 0.4–0.6 per 100,000 women [12]. The etiology of vaginal carcinoma may be age-related. In young patients, the disease seems to be etiologically related to cervical neoplasia and thus HPV dependent. However, in the most common age group, the older patients, there might be another (probably non-HPV-related) etiology associated with hormonal factors and trauma to the vagina [13]. Historically these cancers are more common in elderly and postmenopausal women. If vaginal malignancy is found in younger women, it is usually etiologically linked to cervical cancer, specifically with regard to persistent high-risk HPV infections [14]. *In situ* and invasive vaginal neoplasia share many of the same risk factors with cervical cancer, including a strong relationship with HPV infection. Women who have been treated for a prior anogenital cancer, particularly of the cervix, have a high relative risk, although a low absolute risk, of being diagnosed with vaginal cancer [15]. In addition to exposure to diethylstilbestrol, other environmental factors have been associated with the development of vaginal tumors, including chronic irritation from pessaries, previous hysterectomy for benign disease, immunosuppression therapy, cervical irradiation, and endometriosis. Infectious causes seem to play an even more pernicious role in vaginal cancer [16]. Other known risk factors for vaginal cancer include age at first intercourse at < 17 years old, ≥ 5 lifetime number of sexual partners, immunosuppression, smoking, pelvic radiation therapy, and exposure to diethylstilbestrol (DES) in utero. Women who have had cervical cancer are also at significantly increased risk of developing vaginal cancer. Age is also a risk factor for precancerous lesions of the vagina: high-grade squamous intraepithelial lesion (HSIL)/vaginal intraepithelial neoplasia (VAIN) 2/3 was found more often in women > 50 years old compared to grade low-grade squamous intraepithelial lesion (LSIL)/VAIN 1 (mean age of 45 years). The Centers for Disease Control and Prevention reported that the mean age at diagnosis of vaginal cancer was 69 years, two decades later than the mean age of cervical cancer of 48 years. In summary, hrHPV positivity was found in 99–100% of LSIL/VAIN 1, in 90–96% of HSIL/VAIN 2/3, and in 64–75% of invasive vaginal cancers [17]. Recent findings have suggested that infection with high-risk HPV may increase the risk of developing atheromatous plaques. However, HPV is considered a tissue-specific virus with a strong tropism towards squamous epithelial cells [18].

Cervical cancer and atherosclerosis

Cervical cancer is the fourth most common cancer among women worldwide. In the Unit-

ed States, its incidence and mortality have been declining due to the wide-scale implementation of cytological screening programs [19]. Basic and epidemiologic research conducted during the past 15–20 years has provided overwhelming evidence for an etiologic role for infection with certain types of sexually transmitted HPV as the primary cause of cervical cancer [20]. HPV types 16 and 18 cause nearly 75% of cervical cancer cases, while HPV types 31 and 45 are responsible for 10% of cervical cancers worldwide [21]. The development of cervical cancer is linked to various risk factors, including multiple sexual partners, unprotected sex, and coitus with uncircumcised sexual partners. Other factors include smoking, prolonged use of combined oral contraceptives, and engaging in early sexual practices [21]. The conclusion to an Umbrella Review of Systematic Reviews and Meta-Analyses of Observational Studies stated that there is a strong association between oral contraceptive use, *Chlamydia trachomatis* infection, and increased CC risk [22]. The study demonstrated that individuals infected with *Trichomonas vaginalis* have a higher risk of cervical cancer, especially those co-infected with the human papilloma virus. Also, there is significant regional and racial variation in the correlation between *Trichomonas vaginalis* infection and the risk of cervical cancer [23].

Endogenous sex hormones (estrogens, progesterone) in premenopausal women show cardioprotective effects which result in a lower incidence of CVD; however, the beneficial effect of hormonal replacement therapy has not been sufficiently proven and remains controversial, while it is also associated with adverse effects on the risk of thromboembolism. The current use of oral contraceptives was found to be significantly associated with the risk of venous thromboembolism and ischemic stroke; however, discontinuation of use seemed to result in a rapid return to baseline CVD risk. Sex hormones seem to be a necessary factor for the progression of vaginal HPV infection to malignant disease, and greater exposure to sex hormones, e.g., due to prolonged oral contraceptive use, is associated with increased risk of cervical cancer [24]. The incidence of MI was significantly higher among cervical cancer patients with RT alone or surgery with bilateral oophorectomy alone than among general populations. RT might be a factor in the increased risk of bilateral oophorectomy. Whether RT itself triggers menopause or impairs the ovarian hormone production that increases the risk of MI is unknown [25].

Endometrial cancer and atherosclerosis

Endometrial cancer is the sixth most commonly occurring female cancer [26]. Each year, endometrial cancer develops in about 142,000 women worldwide, and an estimated 42,000 women die from this cancer. The typical age-incidence curve for endometrial cancer shows that most cases are diagnosed after menopause, with the highest incidence around the seventh decade of life [27]. Geographic, socioeconomic, and racial disparities also affect EC incidence and mortality. EC is more prevalent in high-income countries compared with low-income and middle-income countries [26]. Any characteristic that increases exposure to unopposed estrogen increases the risk for endometrial cancer. Because any condition that increases exposure to unopposed estrogen increases the risk of endometrial cancer, tamoxifen therapy, estrogen replacement therapy without progestin and the presence of estrogen-secreting tumors are all risk factors [28]. The EC risk rises with nulliparity, obesity, hypertension, high blood glucose levels, ovulation failure, non-use of hormonal contraceptives, estrogen use, estrogen-producing tumors, and use of tamoxifen [29]. Among women, obesity is more strongly associated with the development of endometrial cancer than any other cancer type. In fact, approximately 57% of endometrial cancers in the United States are thought to be attributable to being overweight and obese [30]. Meta-analyses have demonstrated an independent association between diabetes mellitus and increased risk of EC. Insulin resistance, hyperinsulinemia, hyperglycemia, inflammation, and disturbances in the IGF-1 pathway may contribute to carcinogenesis in individuals with diabetes [26].

Ovarian cancer and atherosclerosis

Ovarian cancer is the sixth most common cancer and the seventh cause of death from cancer in women worldwide and is the most common type of gynecological malignancy [31]. Although ovarian cancer may occur at any age, it is more common in patients older than 50 years. Ovarian cancer has an age-adjusted incidence of 12.5 per 100,000 women [32]. The median age of diagnosis is 63 years. Epithelial ovarian cancer subtypes are infrequently seen in pre-menopausal women (≤ 45 years of age) while ovarian germ cell tumors occur mainly in younger women [33]. The greatest risk factors of ovarian cancer are family history and associated genetic syndromes. Hereditary breast and ovarian cancer syndrome, which occurs in one in every 500 women, is an autosomal dominant mutation in the BRCA1 or BRCA2 gene [32]. As such, factors tending to reduce a woman's ability to ovulate have been linked with a reduced lifetime risk of developing this disease. For example, both the early occurrence of menarche and an older age at menopause have been connected with a possible increased risk [33]. Several modifiable risk factors (e.g., obesity, smoking,

a high-starch or high-fat diet, sedentary lifestyle) are associated with an increased risk of ovarian cancer but have not been established as causes of ovarian cancer. Increased daily fiber intake; the use of carotene, vitamin C, vitamin E, and unsaturated fatty acids; and increased physical activity are moderately associated with a decreased risk of ovarian cancer [32]. Endometriosis is known to predispose individuals towards developing epithelial ovarian cancer (EOC), particularly the clear-cell and endometrioid subtypes, which are known to derive from endometriotic lesions [33]. Multiparity, lactation, oral contraceptive use, and tubal ligation/hysterectomy all decrease a woman's risk of ovarian cancer [34]. A low-fat dietary pattern may reduce the incidence of ovarian cancer among postmenopausal women [35]. Studies of the cellular mechanism of vitamin D in ovarian cancer strongly suggest that it exhibits protective and antitumorigenic activities through genomic and nongenomic signal transduction pathways. These results indicate that vitamin D deficiency results in an increase in the risk of developing ovarian cancer and that vitamin supplements may potentially be an efficient way of preventing cancer [36]. Vitamin D signaling may influence the pathophysiology of atherosclerosis through modulation of the inflammatory response by decreasing the expression of TNFα, IL-6, IL-1, and IL-8 in isolated blood monocytes. Vitamin D deficiency was shown to accelerate the progression of coronary artery disease [37]. Patients with ovarian cancer are often in a hypercoagulable state and have a high risk of venous thrombosis, including deep vein thrombosis and pulmonary embolism [38].

Conclusions

This article demonstrates that correlations between gynecological cancer and atherosclerosis do in fact exist, although concrete etiological connections between the two are hard to establish. Increased telomere length is a predisposing factor for the development of vulvar cancer as well as myocardial infarctions and strokes. HPV virus infections, although tissue-specific, are likely to increase the possibility of atheromatous plaque formation, in addition to being the primary cause of cervical and vaginal malignancies. Furthermore, patients who have undergone radiotherapy or surgery alone, which included bilateral oophorectomy, for cervical cancer, displayed a significantly higher incidence of myocardial infarctions. Regarding endometrial cancer, it has been found that obesity, and the metabolic syndrome it is associated with, constitute independent risk factors for the development of endometrial cancer. Finally, vitamin D deficiency has been shown to contribute to the pathogenesis of ovarian cancer and to accelerate the progression of coronary artery disease.

Conflict of interest

The authors declare no conflict of interest.

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