International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2015): 6.391

Modern Concepts of Ethiological Pathogenesis and Treatment of Endometrial Carcinoma, Research Literature Review

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Abstract: ***Endometrial carcinoma is a frequently diagnosed gynecologic neoplasm on a global scale. Most often it affects females between 50 and 70 years of age. The reasons for development of this disease are many and various, as obesity is one of the leading among them worldwide. It is a chronic, poly-ethiologic disease resulting from the interaction of endogenous and exogenous factors, which is characterized by excessive accumulation of fat in the body due to an increase in the size and/or number of fat tissue. Aim: The objective of this paper is to perform a review of the research literature on the issue of endometrial cancer and changes in the immune systems in these patients.***

Keywords: endometrial cancer, immune system.

1. Introduction

Epidemiology of endometrial carcinoma

Endometrial carcinoma is a frequently diagnosed gynecologic neoplasm on a global scale. Most often it affects females between 50 and 70 years of age. In one third of the patients the disease occurs at a younger age as well. [1].

Every year the US National Cancer Institute registers about 50,000 new cases of endometrial carcinoma, as 8,000 women per annum die with this diagnosis. [2]

A gradual increase in incidence is observed worldwide, Figure 1. According to the latest data from the National Cancer Registry for the year 2012, the registered cases of cervical cancer in Bulgaria are 28.5 per 100,000 women, while the average for Europe are 13.4 per 100,000 women. [3].

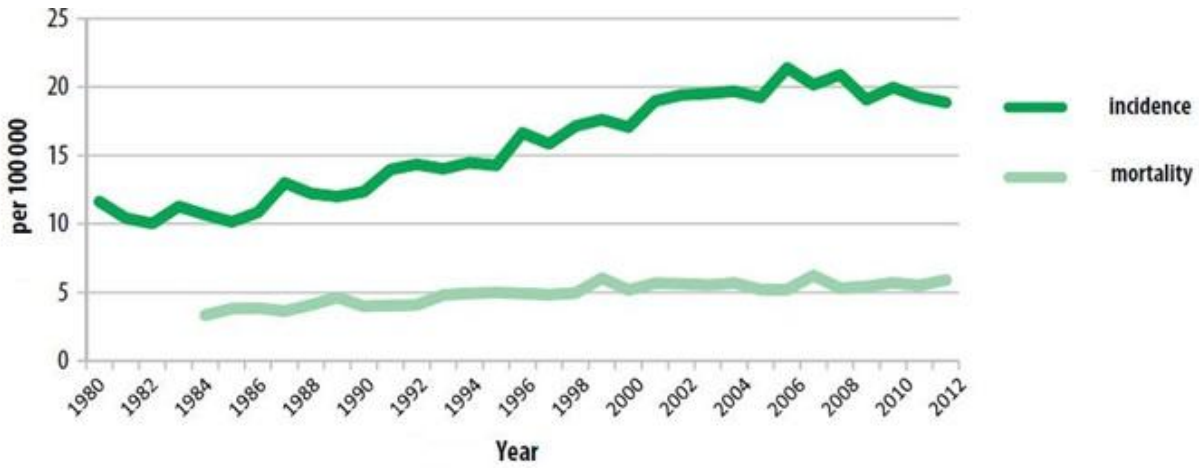

Figure 1: Standardized incidence and mortality (global standard of 100,000) of cervical carcinoma per year of diagnosis.[4]

According to Bulgarian National Cancer Registry the incidence of endometrial and cervical carcinoma is greater in females between 45 and 74 of age, Figure 2. [4]

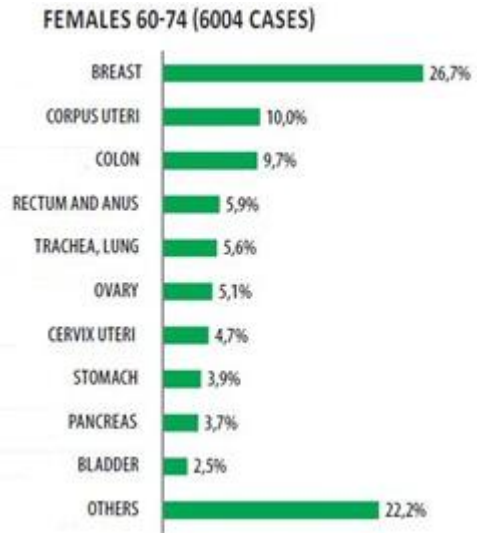

Figure 2: Percentage distribution of the most common malignancies in females in two age groups in Bulgaria, 2012. [4]

The reasons for the above are related to the development of modern diagnostics, as well as to lifestyle and urbanization. Poor eating habits - overeating, consumption of foods suppressing the oxidative processes, endocrine disorders, hypokinesia (reduced physical activity), obesity, etc., all form a prerequisite for the growing incidence of the disease [5], [6], [7], [8], [9], [10]. Malignant neoplasms of the uterus mainly affect the endometrium, whereas malignant tumors originating from the myometrium are considerably less common.

2. Overweight as a leading pathophysiological factor for endometrial carcinoma

The reasons for development of this disease are many and various, as obesity is one of the leading among them worldwide. It is a chronic, poly-ethiologic disease resulting from the interaction of endogenous and exogenous factors, which is characterized by excessive accumulation of fat in the body due to an increase in the size and/or number of fat tissue. Nowadays overweight and obesity are a global problem with expressed co-morbidity and high mortality rate. Bulgaria is ranked sixth in the world in terms of obesity, as obese women are 35%, men - 25%, and children and adolescents between 10-12%. In order to determine the degree of obesity a single method called "Body Mass Index (BMI) is used, which was described in 1896 by Lambert Adolphe Jacques Quetelet. The index is the ratio between weight in kilograms and height in meters squared (BMI = body mass/height, kg/m2). According to the World Health Organization the degree of obesity is precisely determined by the classification of body mass index (BMI), Table 1, Figure 3.

Table 1: Obesity classification by body mass index

Body mass index (BMI)	< 18.5	18.5 –24.9	25.0 – 29.9	30.0 – 34.9	35.0 – 39.9	≥ 40.0
Classification	Underweight	Normal weight	Overweight	Obesity class I	Obesity class II	Obesity class III

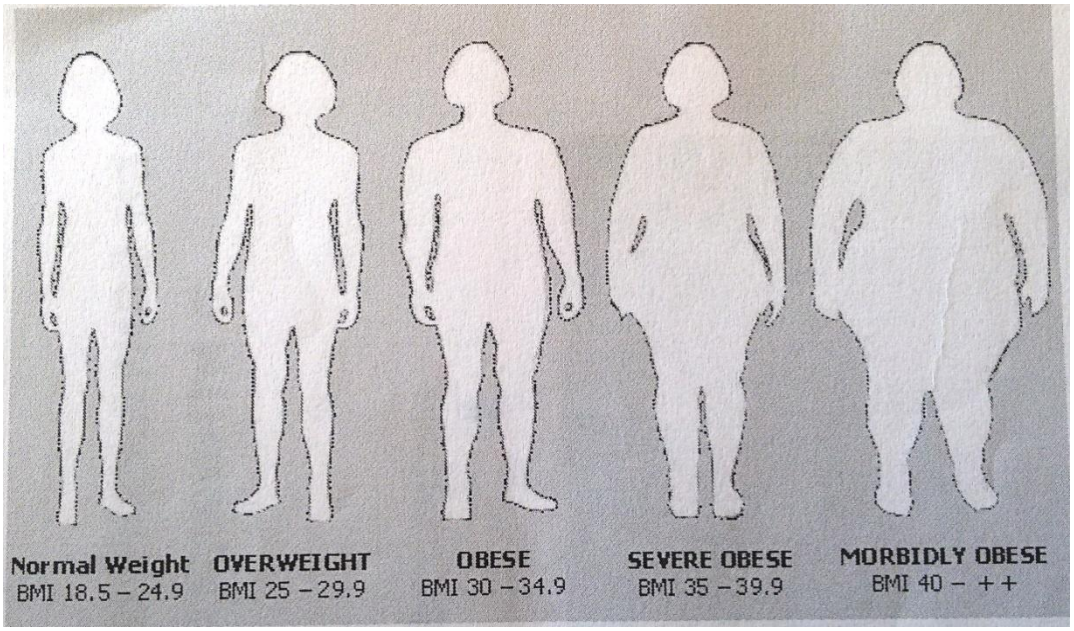

Figure 3: Degree of obesity by body mass index and its impact on the female body

Overweight in females is one of the significant risk factors for predisposition to endometrial cancer - 50% of the cases. [9], [11], [12].

According to multicentre studies conducted in Europe and the United States (International Agency for Research on Cancer (IARC), World Cancer Research Fund, American Institute for Cancer Research), overweight females (BMI> 30kg/ m2) run 3 times higher risk of developing endometrial cancer as compared to women of normal weight.

Several biological mechanisms mediate the link between overweight and endometrial neoplastic risk (cancer risk). In postmenopausal women obesity leads to conversion of androgens, increase in serum bioavailability of estrogens, which are not balanced by progesterone, which in turn

enhances the mitogenic activity of endometrial cells. [13], [14], [15]. Other important factors that are associated with obesity as a prerequisite for development of endometrial cancer are the so-called called *Adipocytokines*. They include:

Adiponectin
It is a specific biological factor secreted by adipose tissue and in low quantity by cardiac myocytes, muscle and endothelial cells. [16], [17], [18].

The function of adiponectin is defined as antiatherogenic, anti-inflammatory and insulin-sensitive. [19].

In contrast to other adipokines, the level of circulation adiponectin has a negative impact - i.e., it reduces obesity, BMI, visceral fat concentration and insulin resistance. [20] A number of studies demonstrate that postmenopausal women have low levels of adiponectin, which favors the development of a number of tumors - breast, colorectal, endometrial carcinoma. [21], [22], [23].

In vitro experiments prove that adiponectin inhibits neoplastic cell proliferation and apoptosis, lowers TNF-α production by macrophages, enhances the production of anti-inflammatory cytokines IL-10 and IL1RA of lymphocytes. [24], [25], [26].

Thus, through the anti-inflammatory and immunomodulatory influence, the anti-cancer effect of adiponectin is attained. Its low level in a number of studies is associated with obesity and increased risk of neoplasm. [21], [27].

Leptin
This is 16 kDA adipokine and it has a very important role in body weight and the body's energy balance through its influence on food absorption and through stimulating energy expenditure. Its circulation level affects the hypothalamic-anorexic neurons and plays a key role on hyperphagia and total BMI. [17], [28], [29].

A strong positive correlation is established between the high level of leptin, overweight, metabolic dysfunction and endometrial carcinoma. [30

There is evidence that leptin enhances cellular neoplastic proliferation in endometrial carcinoma by activating cyclooxygenase 1 (Cox-2).

The high leptin level becomes involved in a vicious circle - progesterone deficiency → hyperinsulinemia → increased endogenous estrogens → increased endometrial carcinomatosis risk → endometrial cancer in postmenopausal patients, known as the so-called "estrogen hypothesis.

Insulin-like growth factor-1
The adipose tissue dysfunction in obese individuals plays a key role in the triggering and development of insulin resistance (obesity-linked hyperinsulinemia.)

Insulin and C-peptide are secreted in equimolar amounts, but C-peptide with its longer lifecycle and smaller fluctuation gives a more accurate idea of the production of insulin, which is secreted by the pancreas. A multicentre European prospective study (European Prospective Investigation into Cancer and Nutrition 2013) establishes a strong association between the pre-diagnostic serum concentrations of C-peptide, insulin-binding growth proteins (IGFBP 1 and IGFB 2), overweight (high BMI) and neoplastic carcinogenic risk. [31] [32] There are several, even though not fully clarified mechanisms, which link etiopathogenetic hyperinsulinemia and endometrial carcinoma:

- Insulin directly stimulates the proliferation of the endometrium;
- Insulin increases IGF1 bioactivity;
- Insulin reduces hepatic secretion and the circulatory level of IGFBP1 and 2, which leads to an increase of androgens and progesterone deficiency, the so-called imbalance of sex hormones in the pre- and postmenopausal period in women. [16], [33], [10], [34], [35]

Adipose Tissue Hypoxia – Oxidative Stress
Oxidative stress may cause imbalance of cellular metabolism and antioxidant stability of cells. [36] [37] Elevated oxidative stress induces intracellular accumulation of peroxide radicals and is an early indicator of the metabolic syndrome with adipose degeneration of the cells. Oxidative stress leads to dysregulation in the production of adipokines, cytokines and chemokines (Adiponectin, Leptin, Resistin, IL-6, etc.).

The role of oxidative stress has a dual significance, and yet authors agree on the fact that oxidative products (ROS) control tumor proliferation and increase the metastatic potential of tumor cells. [24], [38], [39], [40].

Sex hormones and endometrial carcinoma
A number of authors examine adipose tissue as an organ secreting various hormones. [6], [41], [11].

Obesity is associated with increased serum concentration of estradiol, estrogen, and reduced serum concentration of testosterone. During the postmenopause period adipocytes transform androstenedione into estrogen via aromatization. Obese females have 10 times higher levels of estrogens as compared to normal weight females. [35], [42], [43].
Kerschaw EE calls adipose tissue **"an endocrine organ"**.[19]

Adipose tissue elevates insulin, IGF-1, which closes the circle → increased bioavailability of estradiol → reduced testosterone production → increased estrogen neoplastic sensitivity and possible neoplastic breast and endometrium proliferation. [44], [45].

Irrespective what the BMI of patients is, every surgical intervention exerts an influence on the immune system.

Immune system and endometrial carcinoma
When translated from Latin, the word "immunity" means **free**. Everything that is not accepted by the body as "its own", is regarded as a foreign, undesirable load. The basis for recognition of a foreign body and the subsequent defense from it leans on mechanisms of specific and non-specific immunity, which can act both together and separately.

It is well known that nonspecific immunity is genetically conditioned and it does not need a preceding contact with the foreign body. In contrast, the mechanism of specific immunity secures the creation of acquired immunity. [46].

Experimental and clinical studies have demonstrated that surgical trauma entails a change in the immunological response, progressing into the production of proinflammatory cytokines, suppression of cell-mediated immunity and change in programmed cell death, the so-called "apoptosis". [47], [48], [49], [50], [51].

All these unfavorable changes related to the immune system which is being altered not only as a result of surgical stress, but also due to the cancer disease itself, enhance the endeavor of gynecologic oncologists to use such surgical methods that are capable of reducing the frequency of complications, hospital stay and surgical trauma.

High technologies in the treatment of endometrial carcinoma

High technologies in medicine are increasingly entering surgical practice on a wide scale. Their main objective is to achieve greater precision, reduce pain and complications and improve the quality of life in the postoperative period. [52].

This is attained to the greatest extent by robotized surgery performed with da Vinci surgical system. [53]

Robot-assisted laparoscopic hysterectomy with stage-by-stage lymphadenectomy in the treatment of endometrial cancer quickly replaces "open techniques" within a relatively short period after the introduction of the technology in 2005 by a number of surgeries worldwide. [54], [55].

Because of the anatomical and physiological characteristics of extremely obese individuals (BMI> 40 kg/m2), a number of difficulties are observed in performing surgery on organs located in the pelvis. Overweight is a "bottleneck" for the selection of surgical procedure, since the intra- and postoperative complications are more distinct in these patients. [56], [57].

This is precisely what requires the use of minimally invasive surgical techniques whereby the frequency of intra- and postoperative complications is greatly reduced. In indisputable manner, robotic surgery is establishing itself as state-of-the-art surgical technique in recent years.

The advantages of this innovative method are associated with a better opportunity to review the operative field, to reduce operative accidents due to the greater precision in performing the intervention, to decrease hospital stay and blood loss. [58].

Over the past decade the development of laparoscopic and robotic equipment, as well as the use of immunohistochemical methods to prove micrometastases in lymph nodes located in the so-called "strategic place", have all created an opportunity for individual approach in the treatment of oncological diseases, including of the female reproductive system tumors. The sole objective is to reduce postoperative complications and mortality. [59].

The success of robotic surgery in patients with obesity and endometrial cancer is also reported by Tsvetanova at al. [60] (*Dissertation*). The survey conducted by the authors does not register any complications related to the surgery and anesthesia in patients with endometrial carcinoma.

3. Conclusion

Endometrial carcinoma is one of the leading malignancies among women worldwide, causing relatively high mortality rate. Women with this disease are often overweight, which creates a prerequisite for more frequent complications in both the intra- and post-operative period.

Immune system has proven particularly sensitive to surgical trauma. The currently existing modern high-tech surgical methods, leading among which is the robotic surgical system Da Vinci, find successful application in this patient group. This provides a chance not only for more facile postoperative period, but also for a better quality of life of such patients.

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