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Environmental factors and risk for endometrial cancer development

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Summary

Getting to know the most important environmental risk factors for endometrial cancer development lets us provide well programmed primary preventive activity, thus avoiding or greatly reducing environmental risk factors for diseases. This activity may lead to a reduced number of new cases of endometrial cancer. We can help women live longer and better by well programmed preventive activity even when medical knowledge has reached such a high level of development. The authors analysed environmental risk factors for endometrial cancer development based on international medical references. The aim of our work was to review the environmental risk factors for endometrial cancer development which provoke initiation of the disease, sometimes change the clinical stage of the disease and influence medical treatment.

Key words: Endometrial cancer; Risk factors; Cancer development.

Introduction

The number of new endometrial cancer cases in Poland is about 3,000 new cases per year [40]. The most frequent histological type is *adenocarcinoma* (about 60% of all endometrial cancer cases); less frequent is *adenocanthoma* (about 20% of all cases). Other histological types occur less frequently [1, 2].

There are a lot of described risk factors for endometrial cancer which may be responsible for initiation, development, and dynamics of the cancer course. There are two types of prevention - primary and secondary.

Primary prevention consists of getting to know all environmental risk factors that influence initiation and development of the disease. Prevention of the disease is the most effective when risk factors that influence the initiation of processes at the beginning are eliminated. Such preventive activity seems to be the cheapest considering the social costs because the initiation of neoplasms is often avoided.

The aim of secondary preventive activity is to detect a disease early and to properly cure an existing precancer and early cancer states. Consequently this kind of prophylactic treatment is more expensive.

It seems that wide spread primary preventive activity is the best weapon against neoplastic diseases. A well educated society, together with a good presentation of risk factors for endometrial cancer development may be very effective in the reduction of new cancer cases.

Recognizing all of the risk factors and their elimination must coexist with reorientation of life style in every community – i.e., a condition which provides effective preventive activity. Suitable shaping of social health habits is the cheapest way of fighting against neoplastic diseases and the best way for a population to live longer. We hope this presentation of the most important environmental risk factors for endometrial cancer development will help in leading to a suitable social education to lower the total number of new endometrial cancer cases.

Discussion

The mean age when endometrial cancer is mostly detected is about 55-60 years although women may also incur the disease before menopausal age [40]. The literature mostly confirms that endometrial cancer detected before 45 years of age is very rare and such cases are no more than 10% of all detected endometrial

cancers [1, 3]. Some authors suggest that younger women have a better prognosis for recovering than older patients [4, 5].

Patsner [41] says that endometrial cancer cases detected before 45 years of age have lower FIGO clinical stage, and that most detected endometrial cancers before age 45 belong to FIGO clinical Stage I.

Overweight and obesity are basic risk factors that influence the development of the disease. Obese women suffer endometrial cancer far more often than non obese women [1, 6, 7].

Swansson *et al.* [8] confirm that obesity is an important risk factor. Obesity located in the upper body parts is especially unfavourable and makes the risk significantly higher. Obese women were divided into three body mass groups:

1. body mass lower than 58 kg - relative risk defined as 1;
2. body mass higher than 78 kg - relative risk defined as 2.3 times higher than in group 1;
3. body mass higher than 96 kg - relative risk defined as 4.3 times higher than in group 1.

Obesity type was a very important element of Swansson *et al.'s* survey. Obesity of the upper body parts was measured by comparing waist circumference with hip circumference. The authors also measured the skin thickness of the abdomen to tight skin thickness together with hip skin thickness and tight skin thickness. Those measurements revealed a significant correlation of these additional factors for risk of endometrial cancer.

Obesity located in the upper body makes the risk about 5.8 times higher than obesity of another morphology [1, 9, 10].

Obesity type is a risk factor that is not correlated with BMI - body mass index. This relation probably depends on serum SHBG (sex hormone binding globulin) level, which is lower in women with upper body obesity. SHBG serum level inversely correlates with the amount of fat tissue located in the upper body. Low SHBG serum level stimulates a higher production of endogenous estradiol and it also increases the free estrogen serum fraction. Free estrogen serum fraction (not connected with serum proteins) has a higher influence on endometrial proliferation [11].

Other authors claim that obesity type (location) may be correlated with a histological maturity of the neoplasm. A central type of obesity was mostly correlated with better differentiated cancer types with a better prognosis for recovery [12].

Incorrect feeding habits are the most important causes of obesity. Women who have a daily diet with a higher caloric value have a higher risk of developing endometrial cancer [13, 14].

Diet composition is another important risk factor for endometrial cancer. The most dangerous situation is when high caloric meals are correlated with higher intake of fat, oil, meat, eggs and milk [1, 15].

The quality of consumed fats may have an influence on the amount of estrogens absorbed from the digestive tract as well as on their metabolism. It was confirmed that the lowest risk accompanies olive oil [16]. Carbohydrate consumption may reduce the number of detected endometrial cancer cases [1, 17].

A vegetarian diet consisting of fruit and vegetables significantly lowers the risk of developing the disease by lowering serum estrogen levels. The more vegetables that are in the diet the lower the estrogen and prolactin serum levels are. Higher vegetable intake goes with a higher SHBG serum level – which also lowers the free estrogen serum level [1, 17].

Levi *et al.'s* investigations were concentrated on dietary influence on the initiation and development of endometrial cancer. They maintain that intake of a large amount of fats, eggs, meat, beans and sugar may increase a risk of initiation of the disease while intake of corn bread, fruits and noodles is considered to be a protecting factor [18].

Vitamin intake such as beta-carotene and ascorbic acid has a protective influence which is probably correlated with neutralisation of free radicals [19].

There have been single reports issued revealing that women who consume a large amount of calcium more often suffer from endometrial cancer. This may be indirectly correlated with a larger intake of whole milk [20].

All diseases that increase the risk of obesity lead to an increased risk of endometrial cancer and also diabetes mellitus. It is confirmed that about 20% of women suffering from endometrial cancer and also suffer from diabetes [21].

Most of these women have coexisting diseases such as hypertension or arteriosclerosis. It is also known that these diseases coexist with obesity so it is not clear which one plays the main part as a risk factor for endometrial cancer development [1, 21].

Shoff and Newcomb's investigations suggest that diabetes which does not co-exist with overweight does not increase the risk of developing endometrial cancer [6].

Diabetes, hypertension and obesity together form a triad which coexists with at least 60% of cases of endometrial cancer [1, 6].

Other diseases, such as hypothyroidism, increase the risk of obesity; thus hypothyroidism may also increase the risk of endometrial cancer development [22].

Physical activity leading to reduced body mass is an independent positive factor that lowers the risk of initiation of the disease [14, 16].

All sorts of incorrect hormonal secretions that lead to excess serum estrogen levels may increase the risk of the disease. A good example of serum estrogen level excess unbalanced by progesterone is hormonal replacement estrogen therapy administrated to postmenopausal women with an intact uterus. Increased risk correlates with estrogen dose and time of administration [42].

Estrogen therapy, especially with doses of more than 1 mg/day together with one year continuous administration is presumed to be a risk factor. Estrogen therapy with doses less than 0.3 mg/day probably does not have any influence on endometrial cancer development [1, 23, 24]. An analysis performed in 1995 revealed that women who did not take estrogens had a lower risk of developing endometrial cancer compared to women who underwent estrogen therapy. Risk was significantly higher during estrogen therapy and even one year after stopping estrogen intake the risk was significantly higher [1].

Endometrial cancer detected in women who had undergone estrogen therapy had a better prognosis, earlier detected time and better histological type and grade than in women who had not had any estrogen replacement therapy administered. Endometrial cancer in these cases rarely infiltrated the myometrium which correlated with better prognosis for recovery [24, 25].

Estrogen therapy with a progesterone component significantly lowers or even eliminates the risk of endometrial cancer induction - depending on administration time. A 12-day progesterone component during estrogen replacement therapy eliminates the risk of endometrial cancer development but also lowers the benefits that come from estrogen therapy. The progesterone component reduces some benefits that estrogen therapy gives, especially concerning vascular diseases [26].

Oral contraceptive intake reduces the risk of endometrial cancer development, especially compositions with low estrogen and high progesterone doses. A protective effect was observed after a minimum of 12 months of OC-therapy and was observed especially in nuliparous women [26].

Some investigations revealed an increased risk of endometrial cancer development after sequenced OC administration but others did not [27, 28].

Anti-estrogen therapy

Tamoxifen is the most often administered anti-estrogen. Tamoxifen is administered to women suffering from advanced cases of mammary carcinoma. It reduces the number of recurrent cases and lowers the risk of cancer development in the other mammary gland. Tamoxifen also helps in preventing osteoporosis and has a good influence on fat metabolism [1].

In many countries tamoxifen is administered as a preventive factor for women with a high risk of developing mammary cancer [1]. Unfortunately, tamoxifen increases the risk of endometrial cancer development.

One of the largest studies on this thesis was the NSABP where 2,843 patients with mammary carcinoma underwent close investigation. The conclusions of the NSABP study were:

1. The relative risk of endometrial cancer development in women taking tamoxifen is about 2.3.
2. The relative risk of endometrial cancer development in women who suffer from mammary cancer independently on any kind of therapy is about 2.
3. Out of 1,000 women 121.3 may avoid mammary cancer because of tamoxifen therapy.
4. Of 100 women 6.3 will suffer from endometrial cancer while on tamoxifen therapy [1].

Robinson *et. al.'s* study suggests that endometrial cancer cases that develop after tamoxifen administration have a good prognosis for recovery and a better histological type [29]. The Memorial Hospital trial did not confirm these reports [30].

Tamoxifen as an agonist of estrogen receptors may have an influence on estrogen receptors in the myometrium and induce endometrial cancer by that pathway.

Zarbo *et al.* propose annual gynaecological examinations with transvaginal USG or hysteroscopy for women during tamoxifen therapy [43].

Polycystic ovary syndrome (PCO) significantly increases the risk of endometrial cancer development. Women who suffer from PCO always have LH hypersecretion, higher androgen serum levels, anovulatory menstrual cycles (low progesterone levels). Most are obese and suffer many metabolic dysfunctions such as diabetes or hyperlipidemia [31, 32].

Some histological types of ovarian cancer (e.g. endometrial cancer) and rare cases of hormonally active ovarian tumours such as thecoma or folliculoma may increase endometrial cancer risk by imbalanced estrogen over-production [32].

Hepatic cirrhosis lowers the elimination of estrogens from the body so it can increase the risk of developing endometrial cancer [1, 24, 33].

An early age of menarche (before 12 years of age) and menopause after 52 years of age are significant factors which increase the risk of the disease development [1, 34].

Menstrual cycle disturbances, especially connected with anovulatory cycles which lead to an unopposed estrogen influence on the endometrium may increase the risk of endometrial cancer development [1, 35].

Pregnancies and labours were described as protecting factors against development of the disease - one pregnancy and labour make the risk 50% lower [1].

McPherson *et al.* maintain that miscarriage in perimenopausal age not followed by normal pregnancy can lead to an unopposed, prolonged estrogen influence on the endometrium and increase the risk of developing endometrial cancer [35].

Therapy that stimulates ovulation not followed by pregnancy may induce initiation of endometrial cancer. These cases may concern young women before 40 years of age [34, 35].

Obesity, nuliparity and menopause after 52 years of age were together presumed as one factor that increases the risk of developing endometrial cancer by five times [1].

Smoking cigarettes seems to be a protective agent. It was observed especially in women with upper body obesity that smoking reduced the risk of endometrial cancer development four times compared to non-smoking obese women. The more they smoked the lower the risk was, but smoking is generally harmful so it can not be appreciated as a prophylactic activity [36, 37].

Reduction of endometrial cancer development risk ratio was also observed in women with IUD's but the mechanism of this protective action is not known [38].

It was confirmed that black women suffered from worse histological types of endometrial cancer than white women. White women's survivability was about 77% compared to 60% survivability of black women suffering from endometrial cancer. Age of first diagnosis was significantly lower in white than black women. Several studies characterized relative risk of endometrial cancer development for black women as 1.2 which does not have any statistical significance. This result must be compared with other factors such as, for example, living conditions. Race is not an independent risk factor [1, 39].

Conclusions:

1. All diseases and habits that lead to obesity increase the risk of developing endometrial cancer.
2. Estrogens without progesterone balance induce endometrial cancer.
3. Body mass reduction and regulation of estrogen secretions together with regulation of metabolism seem to be basal factors that reduce the risk of developing endometrial cancer.

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