Abstract

Endometrial cancer is one of the most common cancers of the female reproductive organs worldwide, and understanding the cause of the disease is a major challenge for modern medicine. According to the World Cancer Fund, in 2020 there were approximately 417, 000 new cases of this type cancer, and in Poland the incidence was 9,869 cases, making our country one of the leaders in European statistics. Endometrial cancer can be divided into two main types- estrogen-dependent type I, which predominated in perimenopausal or anovulatory women and is often associated with mutations in the pten gene, and type II, a more aggressive type associated with mutations in the tp53 gene. Both types show overactivity of COX-2, an enzyme that plays a key role in inflammatory and neoplastic processes. This singularity of endometrial cancer makes this enzyme an attractive therapeutic and preventive target for the development and progression of the disease. Non-steroidal anti-inflammatory drugs (NSAIDs) can be used to inhibit the activity of this enzyme. In addition to their anticancer effects, these compounds have also been reported to have bactericidal activity, including inhibition of the growth of pathogenic species of the female reproductive organs. These compounds may therefore be a factor in maintaining a normal balance of the organ microbiome and normal levels of COX-2. Unfortunately, long-term use of NSAIDs is associated with the risk of side effects, particularly in the gastrointestinal tract, so it is important to look for new drug modifications. Such modifications may include the introduction of a metal atom into the chemical structure of NSAIDs, which may have the effect of increasing the cytotoxic activity of such compounds against cancer cells. As a result of such modifications, rhenium derivatives of NSAIDs have been synthesized, where rhenium indomethacin and rhenium aspirin showed the potent activity against endometrial cancer cells. The results of the present study indicate significantly higher activity of NSAIDs derivatives against human endometrial cancer cells compared to the original NSAIDs, as well as their significant effect on reactive oxygen species of tumor cells, which may potentially represent a mechanism of indirect induction of cancer cell death.

In recent years, increasing attention has been paid to the endometrial microbiome, which until 2007 was considered to be the microbial-free part of the organ. The literature indicates the presence of taxons, such as *Firmicutes*, *Bacteroides*, *Proteobacteria* and *Actinobacteria* in the microbiome of healthy women,

with a predominance of *Lactobacillus* spp., which considered an indicator of healthy microenvironment. Unfortunately, resent reports only emphasize that the exact composition of the endometrial microbiome could not be determined, which can be related with various relevant factors (method of material collection, body mass index of woman, number of deliveries phase of the menstrual cycle, chosen method of material processing and sequencing, etc.) In turn, significant changes in the balance of the endometrial microbiome have been found in various pathological conditions, including cancer. Changes in the composition of the microbiome can lead to dysbiosis, which may have a potential impact on the pathogenesis of endometrial cancer by the host cell genome destabilization, the epithelial barrier integrity disruption, and activation of toll-like receptors by bacterial metabolites. Our study of comprehensive analysis of smears from the distal part of the cervical canal of women with endometrial cancer and control reported an increased frequency of *Streptococcus*, *Anaerococcus*, *Prevotella*, *Gardnerella*, *Peptoniphilus* and *Porphyromonas* taxa in women with endometrial cancer. *Gardnerella vaginalis* was used for further studies to test the potential effects of explosure of cancerous and nono-cancerous endometrial cells to the pathogenic strain. Interestingly, this species is well known for its ability to promote bacterial vaginosis and is considered highly virulent due to its ability to produce the toxins – vaginolysin, whose production is dependent on the presence of cholesterol in the environment, and sialidase. The results of the study indicate a high level of adhesion of the tested strain to cancerous and non-neoplastic endometrial cells, and a significant effect of the strain presence on increasing levels of reactive oxygen species, mitochondrial activity and levels for the proinflammatory cytokines IL-6 and IL-8. In addition, the obtained results suggest a possible role for *Lactobacillus jensenii* in inflammation relieve of cancer cells, which calls for further studies of the strain in the context of a potential probiotic to support cancer therapy.

In conclusion, the results of the present study have broad implications. The study of the endometrial microbiome, and in particular the pathogenic effect of *G. vaginalis*, provides important data for understanding the mechanisms of endometrial cancer pathogenesis. In addition, the results presented may contribute to new diagnostic and therapeutic strategies for this type of cancer.

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