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ABSTRACT

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PREVENTION OF OVARIAN, FALLOPIAN TUBE, AND PERITONEAL SEROUS CANCERS (LITERATURE REVIEW)

Introduction. This literature review presents an analysis of the incidence and state of prevention of highly malignant tumors that are difficult to diagnose: serous ovarian cancer, primary fallopian tube cancer, and primary peritoneal cancer. In this group of patients, ovarian cancer amounts to 82.0%, fallopian tube cancer – 6.4%, and peritoneal cancer – 10.7%. The problem is very urgent, since, according to the International Agency for Research on Cancer (IARC), more than 225,000 new cases of ovarian cancer alone are registered annually in the world, and more than half of the patients die during the year. No more than 30% of the treated patients survive for up to 10 years. Such poor results are due to the lack of effective methods of prevention and the difficulties of diagnosing this group of diseases.

Methods. The author selected from the world literature more than 45 scientific works on the problems of incidence and prevention of ovarian cancer, primary fallopian tube cancer, and peritoneal cancer and carried out a detailed analysis of them.

Results and Discussion. At the beginning of the 21st century, after a number of morphological, immunohistochemical, and molecular genetic examinations, the global scientific community clearly proved that the root cause of serous ovarian, fallopian tube, and peritoneal cancers is the pathology of the fallopian tube mucosa. Practical observations revealed that women who underwent salpingectomy or tubal sterilization had a much lower risk of serous pelvic cancers. As a result of these examinations and observations, clinical recommendations were made: in order to prevent ovarian cancer, women should be suggested opportunistic bilateral salpingectomy during their operations in the post-reproductive age. Sterilization should be done by removing the fallopian tubes, not by ligation, because of the lower efficiency of the latter. According to

the reports of some authors, this method can reduce the risk of ovarian cancer by 90–98%. There is a lack of reports on the prevention of fallopian tube and peritoneal cancers in the periodical scientific literature, but we can assume that they will not be worse than those for ovarian cancer.

Keywords: ovarian cancer, fallopian tube cancer, peritoneal cancer, morbidity, prevention.

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РЕЗЮМЕ

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ПРОФІЛАКТИКА СЕРОЗНОГО РАКУ ЯЄЧНИКІВ, МАТКОВИХ ТРУБ ТА ОЧЕРЕВИНИ ТАЗУ (ОГЛЯД ЛІТЕРАТУРИ)

Вступ. У даному огляді літератури представлено аналіз захворюваності та стан профілактики складних для діагностики та дуже злоякісних пухлин – серозного раку яєчників, первинного раку маткових труб та первинного раку очеревини тазу. В цій групі хворих по питомій вазі яєчники займають 82,0 %, маткові труби – 6,4%, очеревина тазу – 10,7 %. Проблема дуже актуальна, так як, згідно повідомлень міжнародного агентства по вивченню раку (IARC), в світі щорічно реєструється більше 225 000 нових захворювань тільки раку яєчників, а на протязі року помирають більше половини із них. З числа пролікованих живуть до 10 років не більше 30%. Такі погані результати є наслідками відсутності ефективних методів профілактики та труднощів діагностики цієї групи захворювань.

Методи. Зі світової літератури автором вибрано 45 наукових повідомлень з проблем захворюваності та профілактики раку яєчників, первинного раку маткових труб та очеревини тазу, проведено їх детальний аналіз та зроблені висновки.

Результати та їх обговорення. На початку XXI століття, після проведення низки морфологічних, імуногістохімічних та молекулярногенетичних обстежень, вченими світу було безумовно доведено, що першопричиною серозного раку яєчників, маткових труб та очеревини тазу є патологія слизової оболонки маткової труби. Практичними спостереженнями було виявлено, що в групах жінок, які перенесли сальпінгектомії або перев'язку маткових труб з метою стерилізації ризик захворіти серозними раками органів тазу значно нижче. Підсумком проведених обстежень і спостережень стали рекомендації: з метою профілактики раку яєчників жінкам при операціях в пострепродуктивному віці проводити опортуністичну двобічну сальпінгектомію. Стерилизацію робити шляхом видалення маткових труб, а не перев'язки, тому що ефективність останньої в декілька разів нижча. Згідно повідомлень низки авторів ця методика дозволяє знизити ризик захворювання раком яєчників до 90–98 %. Повідомлення про результати профілактики раку маткових труб і очеревини в періодичній науковій літературі

поки що відсутні, але можна сподіватись, що вони будуть не гірші, ніж раку яєчників.

Ключові слова: рак яєчників, рак маткових труб, рак очеревини тазу, захворюваність, профілактика.

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ABBREVIATIONS

OC – ovarian cancer,
PFTC – primary fallopian tube cancer,
PPC – primary peritoneal cancer

INTRODUCTION / ВСТУП

Until now, the problem of OC, PFTC, and PPC prevention remains largely unresolved. In this group of patients, ovarian cancer amounts to 82.0%, fallopian tube cancer – 6.4%, and peritoneal cancer – 10.7%. Over the past 30 years, various screening and treatment programs have been implemented in the world, including a combination of CA 125 tumor marker and transvaginal sonography, but they did not give the desired results, because the average 10-year survival rate of patients with OC remained < 30% [1, 2, 3, 4]. OC is the second most common gynecologic cancer and the fifth leading cause of death from cancer in women worldwide. According to the International Agency for Research on Cancer (IARC), more than 225,000 new cases of ovarian cancer alone are registered annually in the world, and more than half of the patients die during the year. According to the National Cancer Registry in Ukraine, the number of new cancer patients exceeds 4,000 annually, and at least 2,300 of them die [5, 6, 7]. Such unfavorable results are caused by hidden clinical manifestations of the disease, rapid progression, and late diagnosis. For example, in the USA in 2018, 51% and 20% of newly detected serous OCs had stage III and IV, respectively. For such patients, even after adequate surgical treatment and intensive adjuvant polychemotherapy according to modern clinical protocols, the 5-year survival rate is no more than 20-40%, while for those diagnosed with cancer at stage I, this value reaches up to 90%, and more [1, 2, 7]. The situation is no better with the diagnosis and treatment of PFTC and PPC. For example, reliable preoperative diagnosis of PFTC ranges from 0 to 10–13%, and errors during operations often exceed 50% [8, 9].

Risk groups, morphological features, and causes of tumor formation

The international community has spent much effort on studying ovarian precancer and morphological features of these tumors. No other female organ can compare with the ovary regarding the number and variety of neoplasms. The ovary consists of different types of tissues that perform different structural, hormonal, and reproductive functions. In addition, the ovary comprises about 15 heterotopias and postnatal inclusions, which can become malignant foci. Morphological studies have shown that over 80–85% of ovarian neoplasias are serous adenocarcinomas of various malignancies. Along with serous neoplasms, such cancers as endometrioid tumors, mucous tumors, clear cell and transitional cell tumors, Brener tumors, carcinosarcomas, and other rare neoplasms of an equally malignant nature can develop in the ovary. According to the previously existing theory, serous tumors occur during ovulation due to traumatic lesions and metaplasia of the ovarian surface epithelium, where dysplasia with subsequent invagination and malignancy may occur [9, 10, 11].

The role of ovulation in OC carcinogenesis was first described as an “incessant ovulation” hypothesis in 1971 by M. F. Fathalla and co-authors. They showed a direct relationship between the number of ovulations and the increased risk of ovarian cancer. The risk of OC was significantly lower in multiparous women with large breaks between ovulations afforded by pregnancies and breastfeeding. It was also found that women who did not have ovulatory cycles for more than 10 years due to oral contraceptive use had almost 50% lower risk of OC [9, 12, 13].

However, the origin of serous OC remained unclear for many years, and the search for precancer was unsuccessful. Back in 1961, M. F. Hlazunov noted that this disease should be named “cancer in the ovary” rather than “ovarian cancer”, because the

ovary lacks the epithelium necessary for the development of this kind of tumor [13]. Morphological studies established that malignant tumors of the ovaries consist of elements that, both in terms of histology and genetic mutations, to some extent, resemble epithelium originating from the Mullerian duct. It was also found that serous ovarian tumors contain cells that resemble the epithelium of fallopian tubes, mucous tumors contain cells that resemble mucin-producing glandular cells of the cervical canal, and endometrioid tumors contain cells that resemble the structure of the endometrium [9, 14, 15, 16]. At the end of the 20th century, during a detailed morphological examination of removed fallopian tubes in apparently healthy women with pathological mutations of BRCA-1 and BRCA-2 (familial cancers), secretory cell proliferation with dysplasias and intraepithelial carcinomas were detected, mainly in the fimbrial sections. In addition, accumulation of the p53 tumor suppressor gene was found at the site of dysplasia [17, 18, 19].

In 2003, after a series of studies, J. M. Piek et al. proposed a hypothesis about ovarian serous cancer originating from the fallopian tube epithelium [19, 20, 21]. The hypothesis was confirmed by many authors via morphological, immunohistochemical, and molecular genetic examinations. It was also established that the epithelial layer with p53 mutation and serous tubal intraepithelial carcinoma were identical in patients with sporadic late-stage OC, PFTC, and PPC. Immunohistochemical and targeted sequencing analyses showed that preinvasive PFTC, serous OC, and PPC contained identical p53 mutations [22, 23]. These studies convincingly proved that the source of serous OC, PFTC, and PPC was the fallopian tube epithelium, which implanted inside the ovary – not on its surface layer, as had been previously believed. It was also recognized that endometriosis was a precursor of endometrioid and clear cell carcinomas [10, 25, 26].

In a group of patients operated on serous OC and PPC and having no pathological mutations, Salvador S. et al. found intraepithelial PFTC in 35–70% of cases [20]. This proves the possibility of the preinvasive and initial invasive cancer development in macroscopically unchanged fallopian tubes and in genetically uncompromised patients. The mechanism of serous carcinogenesis and the root causes of serous OC, PFTC, and PPC are related to the epithelial lining of the fallopian tube [20, 26, 27].

Prevention options

T. R. Rebbeck et al. were the first to report that bilateral prophylactic fallopian tube removal reduced the risk of ovarian cancer and breast cancer by 96% in women with BRCA-1 and BRCA-2 mutations [28]. A number of publications soon appeared reporting on the cancer risk reduction after tubal ligation (sterilization), which blocked retrograde menstruation [29, 30, 31, 32].

Retrospective analyses of the results of tubal ligation and tubal removal were conducted in many countries [14, 29, 30, 31, 32]. For example, in Denmark in 2015, Madsen S. et al. conducted a retrospective nationwide analysis covering the period of 1982–2011, including 16,846 women with a history of tubal removal. As a result, this operation made it possible to reduce the risk of OC by 42%. Soon, a number of authors reported that bilateral salpingectomy reduced the incidence of serous OC up to 98% and that it was significantly more effective than tubal ligation [3, 30, 31, 32, 33]. Global scientific studies unquestionably proved the role of the fallopian tubes as the primary cause of the majority of malignant tumors of the ovaries, fallopian tubes, and pelvic peritoneum; they also demonstrated the preventive effect of the widespread implementation of opportunistic salpingectomy (concomitant removal of the fallopian tubes even in women with a low risk of ovarian cancer) [28, 33, 34, 35, 36]. First of all, prevention of these malignant tumors consists in FTC risk groups identification and health improvement measures. The following categories should be identified and treated: women with a genetic predisposition to the disease – based on family history (patients with the BRCA-1 and BRCA-2 gene mutations which can increase FTC risk by up to 30%); women with tubal infertility or chronic inflammatory diseases of the uterine adnexa (especially sactosalpinx-type ones); and patients with endometriosis of the uterine adnexa, which can lead to ovarian cancer. It is necessary to constantly promote repeated childbearing with breastfeeding as well as oral contraception – these factors contribute to the prevention of both FTC and breast cancer.

Obviously, when implementing prophylactic salpingectomy, questions arise regarding its impact on women's health. Previous studies demonstrated that bilateral salpingectomy, as a concomitant operation, took 15 minutes, and sterilization took only 10 minutes of surgical time. During these operations, there were no complications and no need for infusion or blood transfusion. It was also established that in the coming years after salpingectomy, neither a decrease in ovarian reserve, nor a significant impact on the psychophysical condition of women was recorded [33, 34, 37, 38, 39].

The first state that dared to implement the results of these scientific studies on a wide scale (covering the entire territory) was British Columbia, Canada, in 2010. There, a program was developed and implemented for material equipment of medical institutions, training of medical personnel, and general public education not only by medical workers but also by mass media. Gynecologists-surgeons were recommended to do opportunistic salpingectomy in the case of hysterectomy in the post-reproductive age and to perform sterilization by removing the fallopian tubes rather than by ligation. Patients suspected of having "familial cancer" had to be examined for pathological BRCA1 and BRCA2 mutations and rehabilitated in a timely manner. As a result, two years after the start of the program in the province, the number of hysterectomies with fallopian tube removal increased by 3.5 times, and the frequency of tubal ligation decreased from 99.7% to 66.7%. The timing of salpingectomy can vary. If the patient wishes and consents, they can be performed even during cesarean sections. For example, some authors suggest that in women with pathological BRCA mutations, the tubes should be removed after the end of reproductive life, and the ovaries should be removed in premenopause [40]. With modern surgical technologies, this is not a problem, but it increases life's quality and duration.

In the periodical literature, there are already a number of publications about the implementation of this method of ovarian cancer prevention in China, the USA, Italy, France, Austria, and other countries [32, 40, 42, 43, 44]. It is necessary to understand that this is a relatively new and long-term problem. Years, or even tens of years, will pass after widespread implementation of the above-mentioned measures before we obtain final conclusions about the effectiveness and rationality of the proposed method of prevention [32, 43, 45].

CONCLUSIONS / ВИСНОВКИ

Until now, the problem of OC, PFTC, and PPC prevention remains unresolved. A number of morphological, immunohistochemical, and molecular genetic examinations clearly suggested that the root cause of serous ovarian, fallopian tube, and peritoneal cancers is the pathology of the fallopian tube mucosa. In order to provide prevention measures, it was recommended to do bilateral opportunistic salpingectomy in the post-reproductive age and, optionally – to perform sterilization by removing the fallopian tubes. It was suggested to pay special attention to high-risk women with pathological mutations of BRCA-1 and BRCA-2 and to rehabilitate them in a timely manner. According to the latest research by world scientists and practical experience, only comprehensive educational work among the population and implementation of opportunistic salpingectomy will allow a significant reduction in morbidity and mortality due to this group of malignant serous tumors.

CONFLICT OF INTEREST / КОНФЛІКТ ІНТЕРЕСІВ

The authors declare no conflict of interest.

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None.

AUTHOR CONTRIBUTIONS / ВКЛАД АВТОРІВ

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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