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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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GENETIC ALTERATIONS IN TUBO-OVARIAN EPITHELIUM DURING OVARIAN NEOPLASIA

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Abstract.

Background: Ovarian serous carcinomas are a significant cause of female cancer mortality. Emerging evidence suggests a crucial role for the fallopian tube epithelium in the development of high-grade serous ovarian carcinomas (HGSOC), supported by shared molecular alterations like TP53 mutations. However, the precise pathogenetic mechanisms, hormonal influences, and the impact of cancer stem cells and intra-tumoral heterogeneity remain incompletely understood.

Methods: This review synthesizes existing literature, including clinical investigations, epidemiological studies, and molecular analyses, to examine the origins and development of ovarian serous carcinomas. Methodological approaches reviewed include immunohistochemistry, genetic sequencing (e.g., next-generation sequencing), RT-PCR, laser microdissection, and analysis of prophylactic salpingo-oophorectomy specimens.

Results: The review highlights the growing evidence supporting the fallopian tube origin of HGSOC, with frequent co-occurrence of serous tubal intraepithelial carcinomas (STIC) and shared TP53 mutations. Genetic mutations in BRCA1/2, BRAF, KRAS, and PTEN contribute to tumor development. Hormonal influences, particularly estrogen and progesterone receptor expression, and the roles of cancer stem cells (CD117, CD133, CD44) and intra-tumoral heterogeneity are crucial for tumor progression and treatment response.

Conclusion: The fallopian tube epithelium plays a significant role in HGSOC pathogenesis. Further research is needed to elucidate the pathogenetic mechanisms, hormonal influences, and the impact of cancer stem cells and intra-tumoral heterogeneity. A comprehensive understanding of these factors will improve prevention, prognosis, and the development of tailored treatment strategies, including refined classification systems that account for tumor heterogeneity.

Key words. Fallopian tube neoplasms, ovarian neoplasms, tubo-ovarian oncogenesis.

Introduction.

The incidence of primary fallopian tube carcinomas globally ranges from approximately 0.36 to 0.41 per 100,000 women, equating to about 300 to 400 cases each year [1]. Ovarian epithelial tumors consist of a diverse set of neoplastic lesions, predominantly serous (68%), followed by clear cell (13%), endometrioid (9%), and mucinous (3%) types. In 2020, there were 313,959 cases of ovarian tumors and 207,252 deaths reported worldwide, accounting for 3.4% of all female cancers and 4.7% of cancer-related fatalities. About 30% of ovarian cancer cases occur in European nations, while Asian countries show the highest mortality rates [2].

There are three main categories of primary ovarian tumors: germinal/germinal, stromal, and superficial/epithelial tumors [3]. In the first group, the tumor grade ranges from benign, borderline (low malignant potential), and malignant (carcinoma) forms [4]. Ovarian serous carcinomas can be divided into low-grade serous ovarian carcinoma (LGSOC) and high-grade serous ovarian carcinoma (HGSOC).

According to US data, women have a 1.38% risk of developing high-grade ovarian carcinoma, with a median age of diagnosis of 63 years. High-grade ovarian carcinoma is strongly associated with BRCA mutations, and almost all cases involve TP53 mutations [5]. High-grade serous ovarian carcinoma has a poor prognosis, with a mortality rate of more than 70% [6].

There are two histological types of ovarian serous borderline tumors: classic and micropapillary. Classic serous borderline tumor is an epithelial neoplasm consisting of papillae lined by fallopian tube-like epithelium and showing stratification, clusters of single cells, and low-grade nuclear atypia without obvious stromal invasion. Micropapillary borderline tumor is an epithelial neoplasm that shows a sharp transition from central fibrovascular nuclei to long, thin papillae that are five times longer than wide and lined by fallopian tube-like cuboidal epithelium without obvious stromal invasion [7]. Serous borderline tumors account for 4% of all ovarian tumors and 10-15% of serous ovarian tumors. The median age at diagnosis is 42-50 years [8]. Serous borderline ovarian tumors are positive for CK7, PAX8, CA125, WT1, ER, and PR markers [9]. Calretinin and p16 may be negative or heterogeneously positive, and p53 shows wild-type expression (scattered positive cells) [10]. Genetic analysis reveals mutations in the BRAF and KRAS genes with a 95% concordance with serous borderline tumors and associated implants [11].

The ovary originates from multiple embryonic structures, including the coelomic epithelium, subcoelomic mesoderm, primordial germ cells, and yolk sac endoderm. The remaining components of the female reproductive tract, such as the fallopian tubes, uterus, cervix, and upper vagina, arise from Müllerian ducts. This distinct developmental trajectory is underscored by the fact that in patients with Müllerian agenesis, the ovaries typically remain functional. Consequently, the ovary consists of various cell types, each fulfilling specific structural, hormonal, or reproductive roles, leading to different neoplastic processes. For instance, tumors such as granulosa cell tumors and fibromas originate from stromal cells, whereas teratomas and yolk sac tumors stem from germ cells.

Notably, the ovary does not possess a well-defined epithelium but is instead covered by a single layer of mesothelium known as the "ovarian surface epithelium." This layer derives from

the coelomic epithelium rather than the Müllerian ducts and contributes to the serous linings of the fallopian tubes, uterus, and peritoneal cavity. At a molecular level, ovarian surface epithelial cells differ from other differentiated epithelial cells, lacking the expression of carcinoma antigen 125 (CA125) and E-cadherin, which are markers of differentiated epithelium. This distinction raises questions about the mechanisms by which tumors with epithelial characteristics arise in the ovary [3].

Primary carcinomas of the fallopian tube are significantly less frequent than ovarian carcinomas. Research indicates that these tumors often show positivity for CK7, WT1, and p53. The detection rates of fallopian tube carcinomas have risen in recent years, especially in samples from prophylactic salpingo-oophorectomies performed on women with BRCA1 and BRCA2 mutations, supporting the hypothesis regarding the fallopian tube origin of ovarian carcinomas [3,4]. Initial efforts to characterize ovarian carcinogenesis revealed a clear association between ovulation and the risk of ovarian cancer, supported by epidemiological data indicating that women who use oral contraceptives, and thus have reduced ovulatory cycles, experience nearly a 50% decrease in ovarian cancer risk. Conversely, not all epidemiological findings back the theory that uninterrupted ovulation initiates tumors, as evidenced by women with polycystic ovary syndrome, who are at increased risk despite infrequent ovulation [5]. Due to the limitations of the continuous ovulation hypothesis, an alternative explanation has been proposed regarding the malignant transformation of the ovarian surface epithelium.

The gonadotropin hypothesis suggests that excessive stimulation of the ovarian surface epithelium by follicle-stimulating hormone and luteinizing hormone receptors leads to increased cell proliferation, heightening the risk of malignant transformation. Pregnant women and those using oral contraceptives tend to maintain low gonadotropin levels, potentially explaining the heightened risk of ovarian epithelial carcinomas in nulliparous women, those with polycystic ovary syndrome, and other women with primary infertility exhibiting elevated gonadotropin production. Increased gonadotropin synthesis during perimenopause might also elevate the risk of developing ovarian epithelial carcinomas approximately a decade post-menopause.

Despite these hypotheses, plasma levels of follicle-stimulating hormone and luteinizing hormone do not correlate with disease risk in premenopausal or postmenopausal women. Furthermore, while animal studies indicate that gonadotropin exposure can promote tumor growth, definitive evidence linking malignant transformation of the ovarian surface epithelium or cortical inclusion cysts to gonadotropin exposure remains lacking [6].

While several theories attempt to explain the metaplasia and dysplasia of the ovarian mesothelium, a significant gap in our understanding of ovarian carcinogenesis from the ovarian surface epithelium is the identification of a precursor lesion to high-grade carcinoma in the ovary. Progression from benign ovarian cystadenomas to borderline malignant tumors (and subsequently to low-grade malignant carcinomas) is noted, but the transformation from low-grade malignant tumors to high-grade malignant carcinomas is exceedingly rare [7].

In the past two decades, our comprehension of high-grade malignant carcinoma development in the ovary has evolved substantially, primarily due to the identification of BRCA1 and BRCA2 tumor suppressor genes. Approximately 5% to 10% of ovarian cancer cases arise from inherited mutations in these genes [8]. Carriers of BRCA1 and BRCA2 mutations face a 40% to 60% risk of developing ovarian cancer by age 70, in stark contrast to a mere 1.3% risk in the general populace. Consequently, risk-reducing bilateral salpingo-oophorectomy is advised for women with BRCA1 mutations between ages 35 and 40, and for those with BRCA2 mutations between ages 40 and 45.

In the early 2000s, initial reports highlighted epithelial pathologies of the fallopian tubes in samples obtained via prophylactic salpingo-oophorectomy, identified as serous tubal intraepithelial carcinomas (STIC) [9]. In 2005, a standardized protocol for collecting, preparing, and analyzing scrapings from the fimbrial ends of fallopian tubes was established by Brigham and Women's Hospital for routine evaluation in women with BRCA mutations and/or a family history of breast and/or ovarian cancer [10]. This led to an increase in data on serous tubal intraepithelial carcinomas or early serous disease, with early lesions detected in about 2% of prophylactic salpingo-oophorectomy specimens.

Materials and methods.

This review was conducted through a comprehensive analysis of existing literature, encompassing published research, clinical investigations, and epidemiological studies relevant to ovarian carcinogenesis and the fallopian tube's role. The data synthesized originates from a variety of sources. Methodological approaches employed in the reviewed studies include, but are not limited to: immunohistochemical analysis for protein expression profiling (e.g., CK7, WT1, p53, ER, PR); genetic sequencing techniques (e.g., p53 target sequencing, next-generation sequencing) for gene mutation identification (e.g., BRCA1, BRCA2, TP53, BRAF, KRAS, PTEN); reverse transcription-polymerase chain reaction (RT-PCR) for mRNA quantification (e.g., ERα, ERβ, PR); laser microdissection; and analysis of prophylactic salpingo-oophorectomy specimens. Furthermore, the review incorporates epidemiological data to assess ovarian cancer incidence and risk factors, alongside referencing established clinical protocols, such as the standardized fallopian tube sample collection and analysis protocol from Brigham and Women's Hospital. The aim of this review is to provide a comprehensive overview of the current understanding of ovarian carcinogenesis, with a specific focus on the evolving role of the fallopian tube and the clinical implications of recent findings, by analyzing and summarizing the current research and displaying the currently accepted theories.

Results.

This review of existing literature revealed several key findings regarding ovarian carcinogenesis and the role of the fallopian tube. Primary fallopian tube carcinomas were established as significantly less frequent than ovarian carcinomas, while ovarian epithelial tumors were shown to be predominantly serous, followed by clear cell, endometrioid, and mucinous subtypes.

Notably, evidence strongly suggests a fallopian tube origin for high-grade serous ovarian carcinomas (HGSOC), supported by the frequent co-occurrence of serous tubal intraepithelial carcinomas (STIC) in approximately 50% of HGSOC patients and the presence of identical TP53 mutations in both STIC and HGSOC lesions. Molecular analyses highlighted the significant role of TP53 mutations in HGSOC, as well as the involvement of BRCA1 and BRCA2 mutations in increasing ovarian cancer risk. Genetic studies further identified mutations in BRAF, KRAS, and PTEN, contributing to the understanding of tumor development. Histologically, HGSOC was associated with poor prognosis, contrasting with serous borderline tumors, which displayed distinct features and occurred at a younger age. Serous borderline ovarian tumors were characterized by positivity for CK7, PAX8, CA125, WT1, ER, and PR markers. Hormonal influences were also significant, with estrogens promoting carcinogenesis and progesterone exhibiting a protective effect. Variations in estrogen receptor (ER) and progesterone receptor (PR) expression across ovarian carcinoma subtypes were observed, with PR-A loss correlating with malignancy and PR-B labeling index serving as a prognostic factor. Finally, intra-tumoral heterogeneity and cancer stem cells, marked by CD117, CD133, and CD44, were identified as critical factors in tumor progression, treatment resistance, and poor prognosis.

Discussion.

This article presents a comprehensive review of ovarian carcinogenesis, focusing on the evolving understanding of the fallopian tube's role in the development of high-grade serous ovarian carcinoma (HGSOC). The identification of precancerous lesions or early serous carcinoma in BRCA mutation carriers has fueled the hypothesis that serous carcinoma can develop in the ovary or other pelvic sites from the fallopian tubes. This is corroborated by findings that approximately 50% of patients with high-grade malignant serous carcinoma of the ovary have concurrent STIC. Subsequent studies have reported varying frequencies of this association (20% to 60%), which may be due to challenges in identifying intact fallopian tubes likely involved in ovarian masses. A key connection between STIC and serous carcinoma is the presence of somatic TP53 mutations in both lesions, alongside alterations in additional molecular markers like shortened telomeres and cyclin-E amplification [11]. Frequent p53 mutations, and subsequent overexpression demonstrated via immunohistochemistry, are noted in both STIC and serous carcinoma. However, it is also evident that p53 overexpression can frequently occur in the fimbriae of the fallopian tube, irrespective of BRCA status—a phenomenon termed the "p53 signature." Detailed immunohistochemical analyses reveal that the p53 signature is predominantly found in the fimbrial ends of the fallopian tube, particularly in non-ciliated (secretory) cells, and is often associated with STIC. p53 overexpression frequently coincides with γ-H2AX staining, an immunohistochemical marker of DNA double-strand breaks, indicating existing DNA damage. Therefore, p53 overexpression may represent a reactive change due to genotoxic conditions, such as exposure to oxidants in follicular fluid during the postovulatory phase. Notably, in cases of p53 overexpression, other gene mutations are present in 50% of instances, which are analogous or identical to those in STIC [11].

Among the two epithelial cell types in the fallopian tube—secretory and ciliated—the former is less mature and deemed more susceptible to transformation. Secretory cells are also the most sensitive to DNA damage in vitro. p53 overexpression is associated with low proliferative activity, suggesting that DNA damage activates ATM/ATR-regulated signaling pathways, inducing cell cycle arrest. However, as these changes progress to STIC, proliferative activity escalates, evidenced by high Ki67 (MIB1) expression and cytological atypia, along with loss of cellular polarity.

Notably, transitional lesions often arise between p53 overexpression and STIC, displaying intermediate proliferative and morphological traits, referred to as serous intraepithelial lesions (STIL). The existence of these transitional lesions implies that p53 overexpression serves as a precursor to STIC. Some researchers propose that the onset of p53 mutations is preceded by excessive proliferation of secretory cells, typically observed in more proximal regions of the tube compared to those showing p53 overexpression. This area of heightened secretory cell proliferation is believed to consist of at least 30 secretory epithelial cells, acquiring a pseudostratified, benign appearance with low proliferative activity. Occasionally, p53 mutations are detected in these cells, suggesting their potential role as precursors to p53 mutations.

Numerous genetic studies have sought to clarify the molecular connections between precursor lesions in the fallopian tube and high-grade malignant serous carcinomas of the ovary. Utilizing laser microdissection and p53 target sequencing, p53 mutations were identified in 57% of cases, predominantly comprising missense mutations, with identical p53 mutations present in all STIC and STIC/ovarian cancer pairs. However, later studies have also found the same p53 mutations in STIC and high-grade malignant ovarian carcinoma cases [12].

Recent comprehensive genomic analyses employing next-generation sequencing technology revealed a significant correlation between STIC and high-grade malignant ovarian carcinomas. Besides identical p53 mutations, similar modifications were identified in other genes, particularly BRCA1, BRCA2, or PTEN. Nevertheless, pre-existing ovarian cancers also exhibit additional genetic alterations. Evolutionary assessments indicate that p53 mutations and STIC serve as precursors to ovarian carcinoma, defining a seven-year interval between STIC development and the onset of ovarian carcinoma, followed by a rapid potential for metastasis.

It is generally accepted that serous borderline malignant ovarian tumors originate from the ovarian cortex and, unlike high-grade malignant serous carcinomas, do not share a fallopian tube origin [13]. However, this perspective remains unverified and necessitates further exploration, as certain studies have indicated PAX-2 loss in secretory outgrowth cells of the fallopian tube.

The presence of various histological subtypes of ovarian cancer, alongside the complexities of intra-tumoral heterogeneity, enhances the disease's intricacy. Inter-tumoral heterogeneity refers to the genotypic and phenotypic variances

observed among multiple tumors of the same type within an individual patient, such as differences between primary tumors and metastatic lesions or among various metastatic sites. The coexistence of diverse cell populations within a single lesion leads to intra-tumoral heterogeneity, which significantly impacts tumor invasion, metastasis, recurrence, and treatment resistance [14].

Inter-tumoral heterogeneity arises from the clonal expansion of tumor cells, driven by genetic alterations, specifically somatic mutations and stochastic genetic or epigenetic changes. Two principal theories explain the development of intra-tumoral heterogeneity: the clonal evolution theory and the cancer stem cell theory. It is believed that part of tumor heterogeneity arises from stem cells while the clonal evolution model operates in established tumors. As changes accumulate within tumor cell populations, cells with varying and unique properties emerge over time, leading to the eventual development of distinct clones across time and space.

Intra-tumoral heterogeneity encompasses the variability among tumor cells, characterized by different responses to treatment. Research indicates that patients with highly heterogeneous tumors tend to experience lower survival rates following standard treatment. Investigating the heterogeneity of ovarian tumors remains a critical area of study, highlighting the need to collect information to develop suitable personalized treatment strategies. For instance, conventional treatment combining platinum and taxanes is often initially successful, yet resistance typically develops over time.

Cancer stem cells are known to endure treatment conditions, subsequently proliferating and repopulating the tumor with chemoresistant progeny. Supporting this notion, Liu et al. demonstrated that the dissemination of CD44+/CK19+ cancer stem cells correlate with reduced progression-free survival, while Steffensen et al. found that relapses occur more frequently in the presence of early-stage tumor stem cells expressing these markers. Thus, alongside intra-tumoral heterogeneity, understanding the distribution characteristics of cancer stem cells in ovarian carcinoma patients is crucial for prognosis and the development of effective therapeutic strategies.

Several candidate markers are currently utilized to identify ovarian carcinoma stem cells, with CD117 being the first recognized marker associated with ovarian carcinoma stem cells, reflecting tumor formation and poor prognosis. CD133 is another frequently employed marker, linked with various stem cell attributes such as tumor formation, lesion progression, chemoresistance, and poor prognosis, making it a candidate for targeted therapeutic interventions. Additionally, CD44 serves as an important marker for ovarian carcinoma stem cells, associated with tumor formation, lesion progression, and adverse outcomes.

The role of estrogens has long been recognized as a significant factor in ovarian carcinoma development [15]. While estrogen-based oral contraceptives are known to reduce ovarian cancer risk, it is crucial to note that this effect largely stems from a decrease in ovulatory frequency. Estrogen concentrations in ovarian tissue are at least 100 times greater than those in circulation, with levels in the fluid of ovulatory follicles exceeding those in the ovary itself. Studies in breast cancer have demonstrated estrogen's direct genotoxic effects; thus, it is reasonable to assume that genomic damage to ovarian epithelial cells, associated with ovulatory follicles or inclusion cysts, may be partially due to the high estrogen content in follicular fluid or ovarian stroma.

In addition to genetic damage, Syed et al. demonstrated that estradiol-17β and estrone stimulate both normal and malignant ovarian cells via estrogen receptors (ER). Notably, both estradiol-17β and estrone effectively promote the growth of ovarian surface epithelial cells, despite estrone being a considerably weaker estrogen than estradiol-17β. This finding is significant because, in postmenopausal women, estrone is the primary circulating estrogen produced in the skin and adipose tissue through aromatization from androstenedione. A 2022 prospective study indicated that overweight (BMI ≥25) and obesity (BMI >30) correlate with increased ovarian cancer mortality rates, suggesting that peripheral estrogen production may contribute to the progression of ovarian carcinoma.

Research has also illustrated that the mitogenic effects of estrogens, androgens, and gonadotropins on ovarian surface epithelial cells are mediated via the activation of the IL-6/STAT-3 signaling pathway. Ovarian cancer cells are characterized by high levels of persistently activated STAT-3 expression, a known transforming cellular molecule.

A recent investigation revealed that primary cell cultures from ovarian cancer patients secrete estradiol-17β but not testosterone or progesterone. This study also indicated that estrogen exhibits an anti-apoptotic effect on ovarian cancer cells. Ultimately, it can be hypothesized that the combined genotoxic and mitogenic actions of estrogens play a significant role in the neoplastic transformation of normal ovarian surface epithelial cells. Moreover, circulating and/or locally produced estrogens are critical for tumor initiation and progression, as they contribute to growth stimulation while inhibiting apoptosis.

Regarding progesterone, it is considered protective against ovarian carcinogenesis. Loss of heterozygosity at 11q23.3-24.3, where the progesterone receptor (PR) gene locus resides, is frequently identified in ovarian epithelial tumors (~75%) [16]. However, this genetic alteration correlates with a poor prognosis. Epidemiological data further support the protective role of progesterone in ovarian carcinoma development and progression, as an increase in ovarian cancer incidence has been noted in women with progesterone deficiency. Additionally, multiparous women exhibit a reduced risk of developing ovarian cancer, suggesting that the protective effect of pregnancy may stem from heightened progesterone influence on ovarian surface epithelial cells. Evidence also indicates that women with a history of twin pregnancies demonstrate a decreased risk of ovarian carcinoma, likely due to elevated progesterone levels in maternal blood during twin gestation.

Data on the expression levels of estrogen receptors (ER) and progesterone receptors (PR) in ovarian tumors or normal ovarian surface epithelium are limited. Lau et al. utilized semi-quantitative RT-PCR to show the presence of ERα and ERβ mRNA, as well as PR mRNA, in primary cultures of normal ovarian surface epithelial cells. A moderate decrease in ERα mRNA was noted alongside a sharp decline in PR

expression in ovarian carcinoma cell lines compared to normal ovarian surface epithelial cells. Lee et al. reported that 86% of ovarian tumor cases were ER-positive, with 50% PR-positive and 45% exhibiting positivity for both. In another study, PR immunopositivity was observed in the majority of borderline malignant tumors, while nearly all (93%) cases of malignant ovarian tumors were negative for PR. Among various ovarian carcinoma subtypes, ERα immunopositivity was found in 97% of serous adenocarcinomas, 100% of endometrioid adenocarcinomas, 70% of mucinous adenocarcinomas, and none (0%) of clear cell carcinomas. Conversely, ERβ immunopositivity occurred in all ovarian carcinoma subtypes (39% of clear cell carcinomas, 41% of serous adenocarcinomas, 30% of mucinous adenocarcinomas, and 75% of endometrioid adenocarcinomas).

Aside from clear cell carcinoma, PR expression was detected in 30% to 70% of other ovarian carcinoma types. A comparative study of the two main PR isoforms (PR-A and PR-B) in ovarian tumors versus normal and benign ovarian tissues indicated that while there was no significant difference in PR-B expression levels between normal/benign ovarian tissues and cancer cases, PR-A was present in normal and benign tissues but exhibited a marked decrease in malignant tumors. Overall, it appears that the two PR subtypes are differentially regulated by estrogens and show differential expression between normal ovarian surface cells and ovarian carcinoma, with loss of PR-A correlating with malignant ovarian diseases. The reason for the loss of PR-A expression remains unclear, though it may relate to diminished estrogen sensitivity and/or loss of PR heterozygosity in ovarian carcinoma cells.

PROGINS, a complex gene polymorphism of the PR, includes a polymorphism in the G intron of the human PR, resulting from Alu insertion and a G-to-T substitution in exon 4, which causes a valine-to-leucine to change in the receptor region, alongside a C-to-T substitution in exon 5 linked to the Alu insertion. It has been shown that the PROGINS allele is associated with increased PR stability and hormone-induced transcriptional activity. This polymorphism has been linked to ovarian carcinomas in various European and North American Caucasian populations.

Some studies have struggled to establish a strong correlation between ovarian carcinoma progression and PR and/or ER gene expression. However, a recent study indicated that the PR-B labeling index (immunopositivity) serves as an independent prognostic factor for ovarian carcinoma patients [17-27]. Furthermore, it was determined that ER-negative and PR-positive (ER-PR+) ovarian carcinomas, comprising about 10% of all tumors, are characterized by a markedly improved prognosis compared to other combinations of ER and PR expression. The five-year survival rate for patients with ER-PR+ tumors exceeded 80%, while the corresponding rate for tumors with all other steroid hormone receptor expression combinations was approximately 45%.

Conclusion.

This comprehensive review has synthesized a wealth of research to illuminate the complex landscape of ovarian carcinogenesis, with a particular emphasis on the evolving understanding of the fallopian tube's pivotal role. The data presented underscores a paradigm shift in our perception of high-grade serous ovarian carcinoma (HGSOC) origins, strongly suggesting a fallopian tube-centric model. The compelling evidence, including the frequent co-occurrence of serous tubal intraepithelial carcinomas (STIC) with HGSOC, and the shared molecular signatures, notably identical TP53 mutations, supports this hypothesis. However, the intricate interplay between ovarian and fallopian tube pathologies necessitates further rigorous investigation to solidify this connection.

The exploration into the molecular underpinnings of ovarian tumors has revealed a complex interplay of genetic and hormonal factors. The significant role of BRCA1 and BRCA2 mutations in elevating ovarian cancer risk, alongside the identification of other key genetic players such as BRAF, KRAS, and PTEN, highlights the genetic complexity of these malignancies. Furthermore, the hormonal influences, particularly the contrasting roles of estrogens and progesterone, underscore the importance of understanding the hormonal milieu in ovarian carcinogenesis. The observed variations in estrogen and progesterone receptor expression across different ovarian carcinoma subtypes and the correlation of PR-A loss with malignancy emphasize the need for a deeper understanding of these hormonal pathways.

Beyond genetic and hormonal factors, the review has also highlighted the critical role of intra-tumoral heterogeneity and cancer stem cells in tumor progression, treatment resistance, and poor prognosis. The identification of markers like CD117, CD133, and CD44 as indicators of cancer stem cells underscores their potential as therapeutic targets. The recognition that conventional treatments, such as platinum and taxanes, often succumb to resistance due to cancer stem cells and intra-tumoral heterogeneity, necessitates the development of personalized treatment strategies.

Despite the significant advancements in our understanding, substantial gaps remain. The precise mechanisms driving the malignant transformation of the ovarian surface epithelium, the precursor lesions to high-grade carcinomas in the ovary, and the detailed etio-pathogenetic connections between ovarian and fallopian tube tumors require further elucidation. Specifically, the pathogenetic mechanisms of solid tumors, including the proliferative and apoptotic changes in ovarian tumors and the associated fallopian tube epithelium, warrant in-depth investigation to validate or refute the fallopian tube origin theory.

Furthermore, the hormonal influences on neoplastic processes in the fallopian tube remain largely unexplored compared to the well-documented effects in ovarian epithelial tumors. Comparative studies of hormonal receptor expression characteristics in both anatomical regions are crucial. Additionally, a comprehensive understanding of cancer stem cell distribution in both the fallopian tube and associated neoplastic processes, as well as in ovarian epithelial tumors, is essential for developing effective therapeutic strategies.

In conclusion, this review underscores the necessity for continued research to unravel the intricate mechanisms of ovarian carcinogenesis. Future studies should focus on validating the fallopian tube origin of HGSOC, elucidating the hormonal and genetic factors driving tumor development, and characterizing

the role of intra-tumoral heterogeneity and cancer stem cells. Establishing a new classification system for ovarian epithelial tumors that accounts for this heterogeneity will significantly advance personalized treatment approaches. The ultimate goal is to translate these scientific insights into improved prevention, prognosis, and therapeutic strategies, ultimately improving the lives of women affected by these devastating malignancies.

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