

Clues to the origins of ovarian cancer

Family history assessment, genetic screening are key to prevention

by S. DIANE YAMADA, MD, AND SARAH A. ACKROYD, MD, MPH

More than 21,000 women in the United States will receive a diagnosis of ovarian cancer (OC) in 2022. Although ovarian cancer accounts for only 1.1% of new cancer diagnoses, it accounts for 2.3% of all cancer deaths annually and has a 5-year relative survival rate of 49.1%.¹ The median age at diagnosis is 63 years, with the highest incidence of ovarian cancer occurring in White women (11.3 per 100,000), followed by Asian/Pacific Islander women (9.4 per 100,000) and Black women (9.0 per 100,000).¹

The vast majority of ovarian cancers occur in the epithelium, with a smaller fraction originating in stromal cells and germ cells (Table 1, Figure 1¹). The epithelial cancers can be divided into type I and type II tumors. Whereas the type I tumors (endometrioid, clear cell, low-grade serous, and mucinous) typically behave in a more indolent fashion, the type II tumors, primarily composed of

Table 1. Epidemiology of Ovarian Cancer Types¹

Cell type	Frequency of ovarian cancer	Cancer histology	Mean age or age range of diagnosis
Epithelial	65%-70%	Serous adenocarcinoma	56 years
		Mucinous adenocarcinoma	52 years
		Endometrioid adenocarcinoma	50 years
		Clear cell carcinoma	49-55 years
		Carcinosarcoma (mixed)	66 years
Germ cell	15%-20%	Dysgerminoma	10-30 years
		Yolk sac tumor (endodermal sinus)	
		Immature teratoma	
		Choriocarcinoma	
Sex cord stroma	5%-10%	Granulosa cell–adult	Perimenopause
		Granulosa cell–juvenile	< 30 years
		Sertoli-Leydig cell	25 years
Other (metastasis)	< 5%	Krukenberg tumor Brenner tumor Metastasis	Variable

high-grade serous carcinomas, behave much more aggressively with early and widespread dissemination.² Of all

the epithelial carcinomas, high-grade serous carcinoma accounts for 60% to 80% of cases, followed by mucinous



S. DIANE YAMADA, MD, is section chief of gynecologic oncology at University of Chicago Medicine in Illinois.



SARAH A. ACKROYD, MD, MPH, is a gynecologic oncology fellow at University of Chicago Medicine in Illinois.

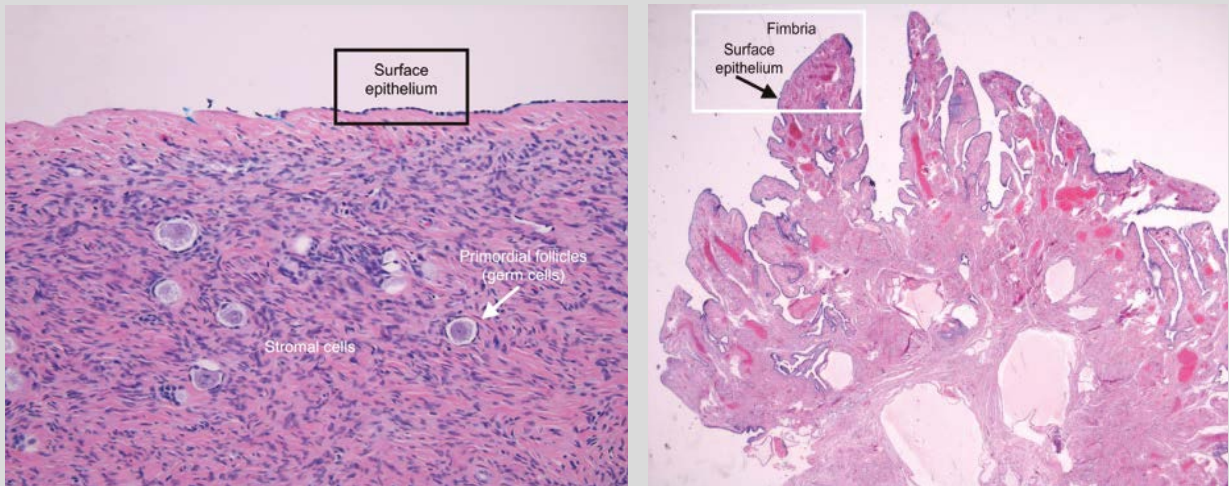


FIGURE 1 A. Ovary H&E magnified 20x with cell types identified¹ **B. Fallopian tube H&E magnified 2x with surface¹ epithelium identified**

H&E, hematoxylin and eosin staining
FIGURES AUTHOR PROVIDED

carcinoma (5%-10%), endometrioid carcinoma (7%-10%), clear cell carcinoma (8%-12%), carcinosarcoma (5%), and other more rarer histologies.³

Symptoms associated with ovarian cancer can be vague. Both the type I and II cancers are associated with abdominal pain, bloating, or gastrointestinal symptoms such as a change in bowel habits.⁴ Patients with symptoms should undergo pelvic/abdominal imaging and serum cancer antigen (CA) 125 testing. Unfortunately, there are no proven diagnostic screening tests (imaging or tumor markers) that have been able to improve early diagnosis or decrease disease-specific mortality.⁵

Origins of ovarian cancer

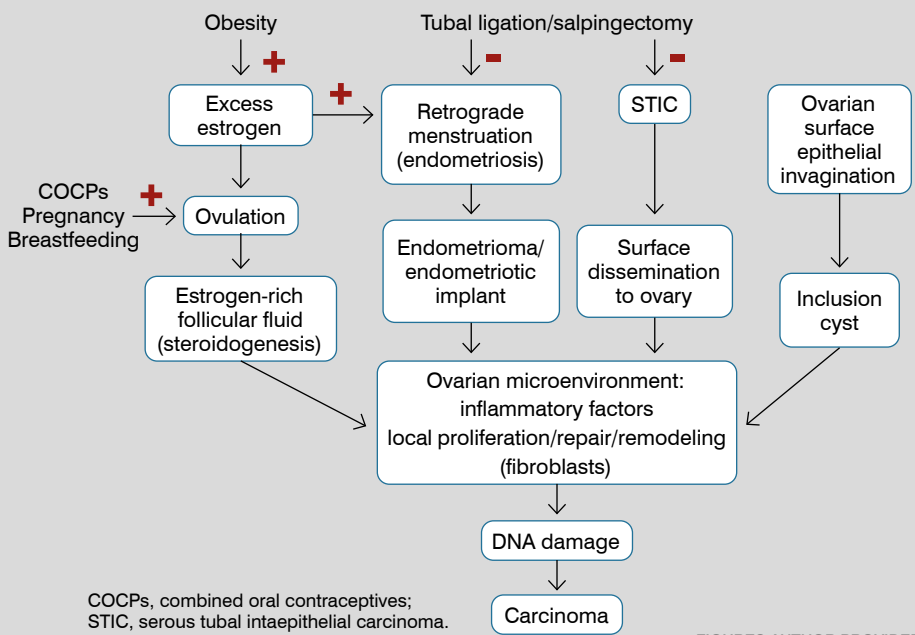
Although theories for development of ovarian cancer have arisen based on knowledge of risk and protective factors, understanding of the sites of origin has been enhanced by knowledge of molecular factors and genetic predisposition. Proposed theories for ovarian carcinogenesis include

incessant ovulation, gonadotropin stimulation, retrograde menstruation, and tubal inflammation. The concepts behind these theories and proposed pathways involved can overlap (Figure 2).⁶ Development from incessant ovulation is a hypothesis that more frequent ovulatory cycles lead to the formation and growth of dominant follicles that produce high levels of estrogen-rich fluid, induce minor trauma from the act of ovulation, and result in surrounding epithelial proliferation, inflammation, wound repair, and increased amounts of DNA damage. Cumulatively, these events are believed to contribute to premalignant transformation. Epidemiologic studies that demonstrate reduced risk of ovarian cancer in women who experience fewer ovulatory cycles due to breastfeeding, pregnancy, or oral contraceptive use provide the most convincing evidence.^{7,8} The same sequence of inflammation and wound repair supports the inclusion cyst theory of ovarian cancer. This theory proposes that ovarian cancer is the result of

ovarian surface epithelium invagination into stromal inclusion cysts that are surrounded by a gonadotropin-rich environment that may induce precursor lesions to become cancer.⁹ Lack of consistent and definitive evidence placing patients undergoing in vitro fertilization at significantly increased risk of ovarian cancer, however, does not bolster the incessant ovulation theory.¹⁰

Convincing evidence points to the fallopian tube as the origin of many ovarian cancer cases. A group of Dutch investigators first reported serous tubal intraepithelial carcinomas (STICs) lesions in prophylactically removed fallopian tubes, many taken from women with *BRCA1* mutations. The most convincing evidence of STIC as a precursor to ovarian cancer is the similar morphologic and molecular (*TP53* mutation) profiles of the STICs and high grade serous ovarian carcinoma lesions.¹¹ Up to 60% of fallopian tubes in patients with ovarian cancer demonstrate STIC at the time of hysterectomy or previous gynecologic surgery,

FIGURE 2. Schematic of Potential Origins of Ovarian Cancer⁶



demonstrating a role as a precursor.² Chronic inflammation of the tubes has also been proposed as carcinogenic based on exposure of the fallopian tube epithelium to retrograde menstruation or infectious and inflammatory agents.¹² Large population studies have demonstrated that occluding the tube via tubal ligation or the patient having had a previous salpingectomy can decrease the incidence of ovarian cancer by 28% and 35% (HR, 0.72, 0.65, respectively).¹³

Endometrioid and clear cell ovarian epithelial cancers are known to be associated with endometriosis. Because of their anatomic location, the fallopian tubes are thought to be integral to the development of endometriosis-related cancers, as endometriotic foci are believed to pass through the tubes to reach the adnexa. Previous studies have identified occlusive tubal ligation as protective against development of

endometrioid/clear cell etiologies, reporting up to a 50% reduction in these histologies, which supports the theory of endometriotic efflux as a potential contributor to nonserous ovarian histologies.¹⁴ Although endometriosis itself is not considered a premalignant condition, there are many components of endometriosis that make malignant transformation plausible. For instance, endometriotic lesions are associated with chronic inflammation and cytokine release that are thought to precipitate the malignant transformation of implants to cancer. Because of overlapping risk factors between endometriosis and ovarian cancer (early menarche, late menopause, nulliparity), the rate of ovarian cancer among patients with known endometriosis is higher than that of the general population. A Swedish study found that compared with controls, patients with

endometriosis were 1.3 to 2.0 times more likely to develop ovarian cancer and to receive a diagnosis at a younger age.¹⁵ Fortunately, given the propensity for development of symptoms, the majority of patients who receive a diagnosis of endometriosis-associated ovarian cancer—commonly endometrioid or clear cell histologies—frequently have stage I disease as compared with the general population who receive a diagnosis of ovarian cancer at stage III or above.¹⁶

General population risk and risk factors

The overall lifetime risk of developing ovarian cancer in the general population is 1.3% to 1.5%, with a majority of cases occurring in the later years of life.¹ Age and family history are the most important risk factors. Events that decrease the number of ovulatory events are known to reduce the risk of ovarian cancer, such as the number of pregnancies (increased protection with more pregnancies), breastfeeding, and use of oral contraceptives.⁸ Taking combined oral contraceptives (COCs) that avert ovulation for at least 5 years can reduce a woman's risk of ovarian cancer by up to 50% over a period of 30 years.⁷

Genetic predisposition to ovarian cancer

Approximately 18% to 24% of patients with ovarian cancer have a genetic predisposition due to inheritance of germline mutations. The widespread use of germline testing on patients with incident cancers has led to the identification of an increasing number of genes associated with cancer. In addition to *BRCA1* and *BRCA2*, *BRIP*, *RAD51C*, *RAD51D*, and *PALB2* have been identified as genes associated with breast or

ovarian cancer. Deleterious mutations in these genes are believed to occur in only 1% of families with a history of ovarian cancer, but if these mutations are present, patients have a 2.5% to 6.0% lifetime risk of developing serous ovarian cancer.¹⁷ Although this risk is higher than that of the general population, most of this cancer risk manifests at older ages. For this reason, risk-reducing salpingo-oophorectomy (RRSO) is typically recommended for patients aged 45 to 50 years.^{17,18} A summary of genetic mutations and overall risk for development of associated cancers is included in **Table 2**.^{5,16-20}

BRCA1/2

The most common germline mutations associated with the development of ovarian or fallopian tube cancer are in *BRCA1* or *BRCA2*, genes involved in the homologous recombination DNA repair pathway. These mutations are propagated in an autosomal dominant fashion. Approximately 16% to 18% of patients with ovarian serous carcinoma have a germline *BRCA* mutation.¹⁹ The risk of ovarian cancer for *BRCA* carriers increases with age. In *BRCA1* carriers, approximately 2% to 3% of cancers develop before 40 years of age, but this incidence increases to 20% by age 50, and increases even more after age 50. Hence, recommendations are for *BRCA1* carriers to undergo bilateral RRSO when they are aged 35 to 40 years.¹⁹ The risk of ovarian cancer in patients with *BRCA2* disease [mutation] is lower than in those with *BRCA1* disease [mutation], with approximately 2% to 3% of cases occurring by age 50, so RRSO is recommended for women aged 40 to 45 years. RRSO has been found to decrease the risk of OC by 75% to 95% but also contributes to the reduction in

Table 2. Genetic Mutations With Predisposition to Ovarian Cancer^{5,16-20}

Genetic predisposition	Mean age of ovarian cancer diagnosis	Most common histology	Preventive surgical recommendation	Risk of ovarian cancer (lifetime)
<i>BRCA1</i>	54 years	HGSOC	RRSO at age 35-40 years	39%-46%
<i>BRCA2</i>	59 years	HGSOC	RRSO at age 40-45 years	10%-27%
Lynch syndrome (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i>)	43 years	Endometrioid (35%)	RRSO after childbearing complete but individualized	10%-13% < 1% by age 40 years
Others <i>BRIP1</i> <i>PALB2</i> <i>RAD51C</i> <i>RAD51D</i>	Not known	HGSOC	Consider RRSO at age 45-50 years	4.1%-12.7% NA 6.1% 13.6%

HGSOC, high-grade serous ovarian cancer; NA, not available; RRSO, risk-reducing salpingo-oophorectomy.

hormone production that is protective against development of breast cancer.²⁰ Although the absolute risk of ovarian cancer is decreased, there is still a small risk of peritoneal carcinoma in *BRCA* carriers. A trial (GOG-0199) by the Gynecologic Oncology Group reported a 2.6% rate of occult STIC or small invasive carcinomas in patients at increased risk who underwent RRSO. This number is thought to reflect the residual risk of peritoneal carcinoma that was not initially detected from RRSO procedures.²¹

LYNCH SYNDROME

Patients with Lynch syndrome (hereditary nonpolyposis colorectal cancer syndrome) are at high risk of developing colorectal cancer and endometrial cancer (up to 70%) in addition to a lifetime risk of developing ovarian cancer that ranges from 10% to 13%.²² Patients with Lynch syndrome are more likely to

develop lower-grade, epithelial histology ovarian cancer and are more likely to develop early-stage disease (85% are stage I or II at diagnosis). Because of their lifetime risk of developing ovarian cancer, RRSO is recommended at age 40 or after completion of childbearing, as the risk of ovarian cancer prior to age 40 is less than 1%.²³

Clinical implications

Understanding the origins of ovarian/fallopian tube cancer and subsequent risk of development of cancer allows for preemptive intervention regardless of whether the patient is desirous of future fertility.

Modifiable risk factors

Although there are no guidelines on preventive interventions to reduce the risk of endometriosis-associated cancers, hormone use is recommended for endometriosis-related

pelvic pain with the goal of reducing estrogen input. Reduction in estrogen exposure to decrease ovulation and endometriotic implant stimulation can theoretically interrupt the inflammatory cascade thought to contribute to ovarian cancer precursors. In the population at increased risk for ovarian cancer, COCP use has been associated with a decreased risk of ovarian cancer in *BRCA1* carriers.²⁴ However, this use must be weighed against the possible risk of breast cancer, which is still unknown.

Genetic counseling and cascade testing

The largest impact in terms of risk reduction occurs in patients or their family members with deleterious mutations conferring increased risk. Germline testing of patients with a new diagnosis of ovarian or fallopian tube cancer can identify mutations that lead to preventive measures and cascade testing of family members. Because of multifactorial causes, uptake of genetic testing has been much less frequent than recommended.

Surgical risk reduction

For women with a family history or genetic predisposition, recommendations exist for prophylactic surgery. For *BRCA1* carriers, given the risk of ovarian cancer at earlier age onset, RRSO is recommended for women aged 35 to 40 years. For *BRCA2* carriers, RRSO

should occur between the ages of 40 and 45 years. For other genes (*BRIP1*, *MLH1*, *MSH2*, *RAD51C*, *RAD51D*) where there is a less than 10% risk of developing ovarian cancer, RRSO is recommended for patients aged 45 to 50 years.¹⁸ The risk of occult malignancy at the time of surgery for *BRCA1* and *BRCA2* carriers is approximately 2% to 10%.

For women at average risk for ovarian cancer, salpingectomy at the time of hysterectomy for other indications or for sterilization may be protective. Data in non-*BRCA* gene carriers who underwent tubal ligation or salpingectomy have demonstrated up to a 35% risk reduction for ovarian cancer.¹³ But in women 50 years or younger, the risk of all-cause mortality makes salpingo-oophorectomy less advisable unless there is a significant family history of ovarian cancer.²⁵ This, in conjunction with the knowledge that a significant proportion of cancers may arise from the fallopian tubes, raises the question of salpingectomy for risk reduction. The prospective SOROCK trial (NCT04251052) examining elective bilateral salpingo-oophorectomy (BSO) or salpingectomy in *BRCA1* carriers is underway to assess this.

Bilateral RRSO in women with a genetic predisposition or family history of ovarian cancer has been shown to decrease the risk of ovarian cancer by up to 95%.²⁰ Approximately 3% to 8% of women who undergo RRSO for genetic predisposition will have an incidental

STIC lesion found on permanent pathology, but women who have BSO for benign indications have incidental rates of less than 1%.²⁶ If STIC lesions are identified incidentally, comprehensive evaluation of the abdominal cavity and peritoneal washings should be performed to ensure there is no evidence of disseminated disease. However, there are no definitive recommendations for surgical staging if a STIC lesion is incidentally found; in fact, the largest study examining outcomes in isolated STIC in RRSO patients reports limited utility of surgical staging because clinical outcomes associated with observation were favorable.²⁷ Once identified, management with surveillance pelvic ultrasound and CA125 testing are reasonable approaches to monitoring.

Conclusion

The most important aspects of gynecologic care in the prevention of ovarian/fallopian tube cancer are extensively reviewing family history and facilitating cascade genetic testing for patients and families identified with genetic mutations. Use of COCPs is associated with risk reduction even in carriers of genetic mutation and curb inflammation that contributes to risk in disease entities. Salpingectomy has been associated with reduced risk of cancer but its contribution compared with RRSO is currently under study in carriers of genetic mutations. ■

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■ Theories suggest that incessant ovulation, inflammation, and tubal lesions contribute to the development of ovarian cancer.

■ Approximately 18% to 24% of patients who receive a diagnosis of ovarian cancer have an inherited germline mutation.

■ Risk-reducing bilateral salpingo-oophorectomy in patients with a predisposition to ovarian cancer decreases the risk of ovarian cancer by up to 95%.

■ In the general population, combined oral contraceptive use for a duration of at least 5 years can reduce the incidence of ovarian cancer by up to 50%.