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REVIEW

Global epidemiology of ovarian cancer: patterns, trends, and risk factors

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ABSTRACT Ovarian cancer was the eighth most frequently diagnosed cancer among women in 2022. The global age-standardized incidence rate of ovarian cancer decreased from 7.22/100,000 to 6.71/100,000 from 1990 to 2021. However, incidence trends varied across countries. Declining ovarian cancer incidence rates were reported in high-income countries, such as the United States, Austria, the Netherlands, and Norway, while there were increasing incidence rates in Africa and parts of Asia, including Japan and India. The global age-standardized mortality rate of ovarian cancer decreased from 4.73/100,000 to 4.06/100,000 between 1999 and 2021 with varying trends among countries. Moreover, the age-standardized 5-year net ovarian cancer survival rate in most countries remained < 50%. Several specific factors related to ovarian cancer risk have been identified, including reproductive factors, use of oral contraceptives, anti-inflammatory diets, endometriosis, pelvic inflammatory disease, obesity, diabetes, and occupational asbestos exposure. No screening or prevention strategy has been proven effective in downstaging or reducing mortality from ovarian cancer in an average-risk population without a family cancer history or pathogenic variants. Indeed, risk-reducing salpingo-oophorectomy remains the gold standard for lowering the risk of ovarian cancer in high-risk individuals with hereditary mutations. This review provides a comprehensive overview of the epidemiology, risk factors, screening, and prevention of ovarian cancer, aiming to offer a global perspective on public health strategies for addressing the disease.

KEYWORDS Ovarian cancer; epidemiology; risk factors; trend; prevention; screening

Introduction

Ovarian cancer ranks as the eighth most frequently diagnosed cancer and the eighth leading cause of cancer-related deaths in women worldwide. An estimated 324,603 women were diagnosed with ovarian cancer in 2022 and 206,956 died of the disease according to GLOBOCAN 2022[1]. The global number of ovarian cancer cases and deaths is projected to increase by 46.9% and 62.7%, respectively, reaching 476,912 cases and 336,637 deaths by 2050[2]. Although there have been advances in ovarian cancer screening, detection, and treatment methods over the past several decades, particularly targeted therapy and immunotherapy[3], ovarian cancer remains largely incurable with a 5-year net survival < 50% in most countries[4]. The substantial disease burden underscores the public health significance given the persistent challenges in treating ovarian cancer. A structured search of PubMed, Web of Science, and EMBASE (January 1990–May 2025) was performed using terms related to ovarian cancer epidemiology, risk factors, screening, and prevention. Peer-reviewed original studies, pooled analyses, meta-analyses, and large population-based investigations were included, while non-English publications, case reports, conference abstracts, and studies lacking methodologic detail were excluded. Additional sources were identified through manual reference screening. This review presents the most recent and comprehensive evidence on the epidemiology, risk factors, screening, and prevention of ovarian cancer with the aim of enhancing global understanding and informing public health strategies to reduce the burden of disease.

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Pathologic classification of ovarian cancer

Ovarian cancer encompasses a heterogeneous group that originates from epithelial and non-epithelial cells, resulting in two major subtypes (epithelial and non-epithelial ovarian cancer). Each subtype is characterized by distinct origins, pathologic features, epidemiologic patterns, and risk factors.

Epithelial ovarian cancer is the most common form, accounting for 90%–95% of all ovarian cancers[5,6]. Epithelial cancer is classified histologically into serous (52%), endometrioid (10%), mucinous (6%), clear cell (6%), and unspecified subtypes (approximately 25%)[7]. Low-grade serous carcinomas are thought to originate from fallopian tube epithelium (endosalpingiosis) or serous ovarian borderline tumors, whereas endometrioid and clear cell carcinomas originate from endometrial tissue (endometriosis)[8]. Most mucinous carcinomas are believed to derive from transitional epithelium at the tuboperitoneal junction[9].

Epithelial ovarian cancer can be further grouped as type I or II ovarian cancer according to clinicopathologic and molecular characteristics[9]. Type I epithelial ovarian cancers are generally low-grade and indolent, genetically stable, large, unilateral, cystic tumors that are confined to the ovary and are believed to develop from extraovarian benign lesions. Type II epithelial ovarian cancers typically present in an advanced stage and are high-grade bilateral types with aggressive behavior and lethal survival. Type II epithelial ovarian cancers are thought to originate as fallopian tube fimbriae carcinomas that spread to the ovaries and/or peritoneum[9,10].

Non-epithelial ovarian cancer consists of sex cord-stromal tumors (e.g., granulosa cell tumors and thecomas) and germ cell tumors (e.g., teratomas and dysgerminomas). These subtypes are relatively rare and occur more frequently in younger women.

The endometrioid subtype of localized and regional epithelial ovarian cancer exhibits the most favorable prognosis, followed by low-grade serous and mucinous ovarian cancer. Ovarian carcinosarcoma is associated with the poorest prognosis with a 5-year survival rate < 50%. However, distant-stage ovarian cancer, which accounts for the majority of diagnoses, presents a comparatively worse prognosis. Within these classifications, low-grade serous, endometrioid, and high-grade serous ovarian cancer have the best prognosis, followed by clear cell and mucinous subtypes. Ovarian carcinosarcoma has the worst histology of ovarian cancer[6].

Descriptive epidemiology and time trend of the cancer burden

The global annual incident cases of ovarian cancer reached 324,603 in 2022 according to GLOBOCAN[1]; the geographic incidence variation differed worldwide. The highest age-adjusted incidence rates for ovarian cancer were in Eastern Europe at 11.0/100,000, followed by Northern Europe (9.1/100,000), Southern Europe (8.4/100,000), and South-East Asia (8.1/100,000). The lowest age-adjusted incidence rates for ovarian cancer were in Middle Africa (4.3/100,000), Southern Africa (4.9/100,000), and the Caribbean (4.9/100,000). Detailed data for each region are shown in **Table 1**.

Countries with a very high human development index (HDI) had the highest age-adjusted incidence rates for ovarian cancer (8.2/100,000). Low HDI countries had the lowest incidence rate for ovarian cancer (4.9/100,000). The global age-standardized incidence rate for ovarian cancer declined from 7.22/100,000 to 6.71/100,000 from 1990 to 2021 with an estimated annual percentage change of −0.38 [95% confidence interval (CI), −0.43 to −0.32][1,11]. Detailed data from 2005–2016 revealed a decreased incidence rate for ovarian cancer in Australia, the USA, Denmark, Sweden, Germany, France, Colombia, and Norway, which was due, at least in part, to the increased use of oral contraceptive pills and the decreased administration of menopausal estrogen-only hormone therapy[7,12]. In contrast, the incidence rates for ovarian cancer in Eastern Europe and some regions of Asia have been increasing, particularly in Belarus, Japan, Thailand, and India[12,13]. Of note, the lower use of oral contraceptive pills and lower parity might partially explain the increasing rates[14]. Statistics in China showed the age-standardized incidence rates for ovarian cancer were relatively stable from 2011–2018[15].

The global new deaths from ovarian cancer have reached 206,956 according to GLOBOCAN 2022. Regionally, the highest age-adjusted mortality rates for ovarian cancer were also in Eastern Europe (6.1/100,000), followed by South-East Asia (5.1/100,000), and Northern Europe (4.8/100,000). Eastern Asia had the lowest age-adjusted mortality rate for ovarian cancer (2.7/100,000). Countries with a medium HDI had the highest age-adjusted mortality rate for ovarian cancer (4.5/100,000), while the high HDI countries had the lowest mortality rate (3.3/100,000). The global age-standardized mortality rate for ovarian cancer declined from 1999–2021 by an estimated annual percentage change of −0.62 (95% CI, −0.68 to −0.57)[11]. The mortality rate of ovarian cancer in the USA declined between 1976 and 2015 by 33.0%[7]. However, the mortality rate for ovarian cancer in China showed an upward trend with an average annual percentage change of 4.4% from 2000–2018[15].

The age-standardized 5-year net ovarian cancer survival rate in most countries was still < 50% for women diagnosed from 2010–2014 according to the CONCORD-3[4]. Survival rates for ovarian cancer ranged from 40.0%–49.0% in Canada, the USA, China, Japan, Korea, Singapore, Austria, Finland, France, Germany, Iceland, Norway, Portugal, Sweden, Switzerland, and Australia. Survival rates for ovarian cancer were < 30% in Chile and < 20% in India. The

Table 1 Age-standardized ovarian cancer incidence and mortality rates in 2022

World	Incidence				Mortality			
	Number	ASR	Crude rate	Cumulative risk	Number	ASR	Crude rate	Cumulative risk
Region								
Northern America	24,484	7.5	13.0	0.83	15,554	3.8	8.3	0.44
Central America	6175	6.0	6.6	0.64	4033	3.9	4.3	0.44
South America	16,447	5.6	7.4	0.62	10,866	3.5	4.9	0.41
Eastern Africa	7690	5.3	3.3	0.60	5518	4.2	2.3	0.50
Middle Africa	2458	4.3	2.6	0.45	1794	3.5	1.9	0.39
Northern Africa	7145	6.0	5.6	0.66	4687	4.0	3.7	0.48
Southern Africa	1677	4.9	4.8	0.55	1424	4.2	4.1	0.47
Western Africa	6790	5.1	3.2	0.54	4601	3.8	2.2	0.43
Caribbean	1450	4.9	6.5	0.53	1012	3.2	4.5	0.36
Eastern Asia	75,773	6.0	9.5	0.64	40,264	2.7	5.1	0.32
South-East Asia	32,113	8.1	9.4	0.85	20,514	5.1	6.0	0.58
South Central Asia	61,931	6.1	6.2	0.67	42,839	4.3	4.3	0.51
Western Asia	8406	6.1	6.1	0.66	5930	4.3	4.3	0.51
Eastern Europe	29,416	11.0	19.0	1.2	19,165	6.1	12.4	0.73
Northern Europe	9787	9.1	18.1	1.0	6586	4.8	12.2	0.56
Southern Europe	13,265	8.4	17.1	0.93	8398	4.1	10.8	0.48
Western Europe	17,004	7.1	17.0	0.81	12,083	4.1	12.1	0.48
Australia-New Zealand	2177	8.0	14.0	0.89	1384	4.0	8.9	0.46
Melanesia	359	7.5	6.4	0.77	262	5.8	4.6	0.64
Micronesia	22	7.3	7.9	0.91	19	6.4	6.9	0.83
Polynesia	34	9.0	10.0	1.1	23	6.0	6.7	0.76
HDI level								
Very high HDI country	120,904	8.2	14.6	0.91	77,625	4.3	9.4	0.51
High HDI country	113,283	6.0	8.3	0.65	66,974	3.3	4.9	0.38
Medium HDI country	70,820	6.4	6.4	0.70	48,669	4.5	4.4	0.53
Low HDI country	19,477	4.9	3.2	0.53	13,590	3.7	2.3	0.43

ASR, age-adjusted rate, per 100,000 person-years; HDI, human development index.

survival trend for ovarian cancer has remained relatively flat between 1995-1999 and 2010-2014[4,16]. Improvements in 5-year survival for ovarian cancer were reported across 17 countries, including the USA, Japan, Korea, Bulgaria, the Czech Republic, Denmark, France, Ireland, Italy, the Netherlands, Norway, Poland, Portugal, Spain, Switzerland, the UK, and Australia. The most remarkable improvement in survival for ovarian cancer was observed in Japan with an increase of 11.1%; detailed data are shown in **Figure 1**. The updated age-standardized 5-year relative survival rate for ovarian cancer in China between 2019 and 2021 was 39.6%; the rate was stable from 2008–2021[17]. The 5-year relative ovarian cancer survival rate in the US increased from 44.6% to 52.8% between 2000 and 2017 with an average absolute increase of 0.4% according to the SEER database of 21 registries[18].

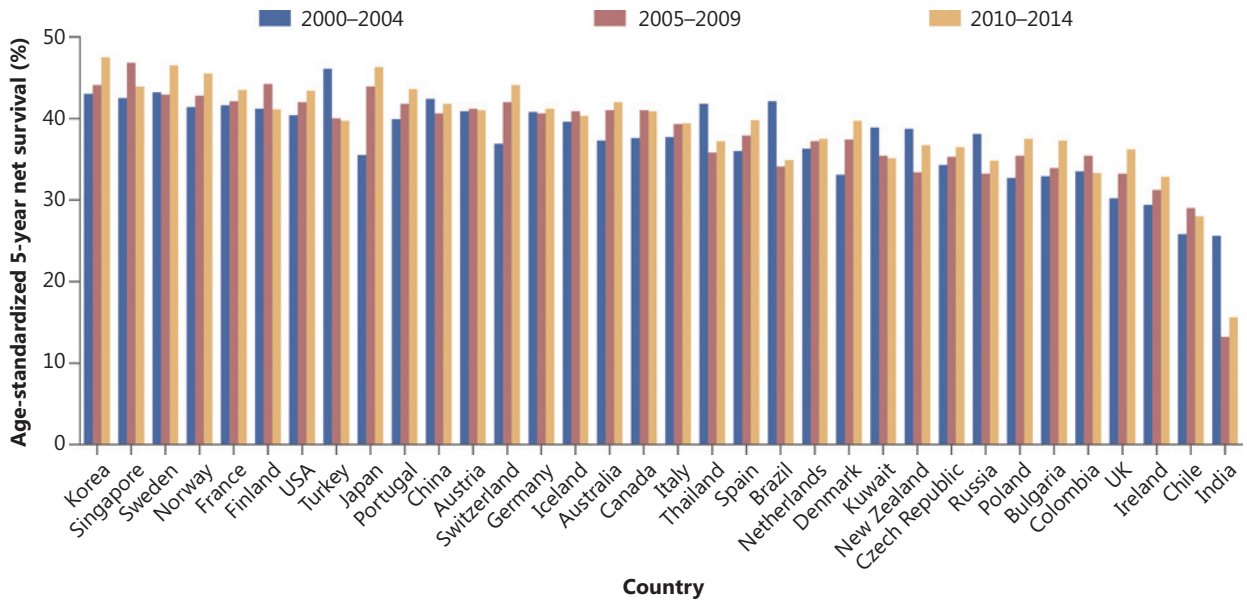


Figure 1 Age-standardized 5-year net ovarian cancer survival in different countries from 2000 to 2014. This figure illustrates the geographic and temporal variations in ovarian cancer survival across select countries. A key box above the graph explains the colored lines representing different time periods. The x-axis shows the countries sorted from highest-to-lowest average survival rate. The y-axis shows the age-standardized 5-year net survival rate expressed as a percentage (%).

Disability-adjusted life years and years lived with disability

Table 2 illustrates the disability-adjusted life years (DALYs) and years lived with disability (YLDs) for ovarian cancer[19]. The global DALYs count reached 5,160,000/100,000 in 2021. The European region had the highest DALYs count (1,260,000/100,000), followed by South-East Asia (1,130,000/100,000) and the Western Pacific region (1,120,000/100,000). The Eastern Mediterranean region had the lowest DALYs count (320,000/100,000). The global DALYs for ovarian cancer increased from 1990 to 2021 (**Figure 2A**).

The global YLDs count rose to 155,650/100,000 in 2021. The regional distribution of ovarian cancer YLDs was comparable to DALYs. The European region had the highest YLDs count (38,100/100,000), followed by the Western Pacific region (37,280/100,000) and South-East Asia (33,320/100,000). The Eastern Mediterranean region had the lowest YLDs count (8300/100,000). The global YLDs trend for ovarian cancer also exhibited a similar increase from 1990–2021 (**Figure 2B**).

The age-specific DALYs counts in 2021 are shown in **Figure 3A**. The DALYs counts increased with advancing age at the time of diagnosis. Women > 70 years of age had the highest DALYs count (1,130,000/100,000). The age-specific YLDs counts in 2021 are shown in **Figure 3B**. The YLDs increased with advancing age at the time of diagnosis. However, it is worth noting that both DALYs and YLDs counts declined in women who were diagnosed between 60 and 69 years of age, which may be attributed to the use of oral contraceptives[12].

Risk factors for ovarian cancer

Several factors have been shown to be associated with the risk of ovarian cancer, including reproductive, behavioral, dietary, metabolic, medical, genetic, and environmental factors (**Table 3**, **Figure 4**). The risk estimates presented in **Table 3** were extracted from published meta-analyses or pooled studies, each of which used a multivariable-adjusted analytical framework as reported by the original authors. Because effect modifiers and confidence intervals were not uniformly available across studies, these values should be interpreted as summarized associations rather than harmonized effect sizes derived from a single analytical model.

Reproductive factors

Studies have shown that childbirth has a protective effect on epithelial ovarian cancer and the effect is subtype-dependent. The risk of ovarian cancer decreased by 6% [relative risk (RR), 0.94; 95% CI, 0.92–0.96] with each additional birth among women who have had children in a prospective study involving 1.1 million UK women with the greatest reduction

Table 2 Ovarian cancer DALYs and YLDs in the global burden of disease study 2021

Location	DALYs per 100,000			YLDs per 100,000		
	Value	Lower bound	Upper bound	Value	Lower bound	Upper bound
Africa	357,474.21	266,133.78	427,989.60	8,835.35	5,890.77	12,014.81
South-East Asia	1,132,285.22	966,868.25	1,372,584.52	33,318.56	23,436.52	44,561.70
Americas	944,236.63	889,096.85	990,123.33	28,354.09	20,965.35	36,478.54
Europe	1,263,327.45	1,177,992.02	1,332,170.16	38,099.13	28,070.04	48,972.54
Eastern Mediterranean	315,571.69	235,103.98	406,673.99	8,378.60	5,684.23	11,920.54
Western Pacific	1,120,217.11	896,904.74	1,364,393.88	37,279.62	25,724.54	51,643.26
Global	5,163,256.30	5,608,304.11	4,692,422.55	155,645.72	201,143.40	113,442.62

DALY, disability-adjusted life years; YLD, years lived with disability.

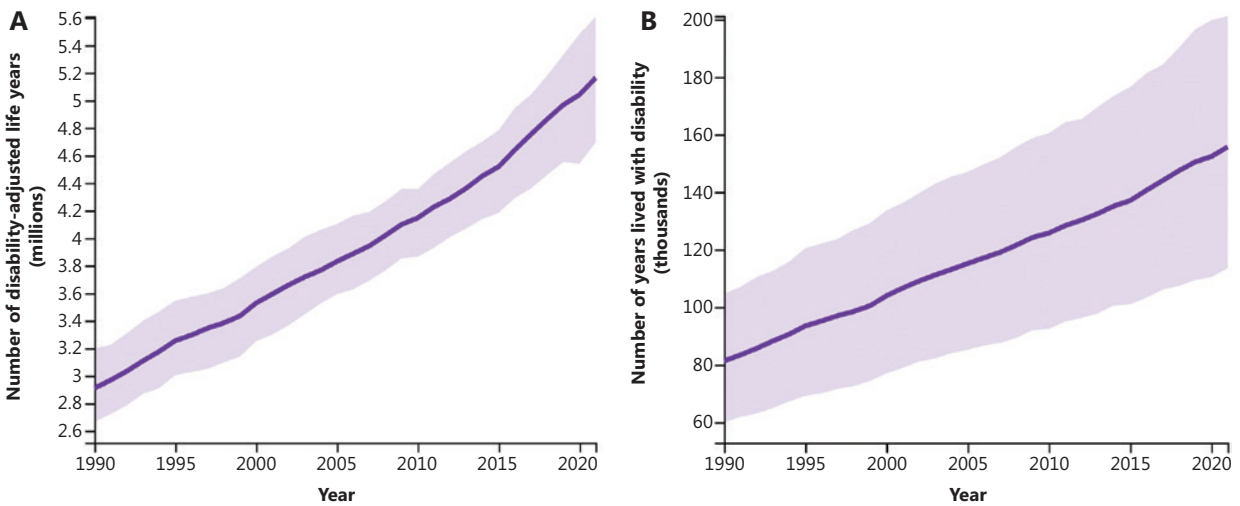


Figure 2 Global trends in disability-adjusted life years (DALYs) and years lived with disability (YLDs) due to ovarian cancer (1990–2021). This figure presents the global disease burden of ovarian cancer over three decades, as measured by DALYs (A) and YLDs (B). The global trends in DALYs and YLDs from ovarian cancer showed an increasing trend from 1990 to 2021.

in the risk of clear cell carcinoma (RR, 0.75; 95% CI, 0.65–0.85)[20]. However, in a Finnish cohort study involving 87,929 multiparous women, multiparity (> 5 births) did not provide additional protection against ovarian cancer[37]. In summary, these findings indicated that while the number of pregnancies is negatively correlated with the risk of ovarian cancer, this protective effect does not follow a linear dose-response relationship with the number of pregnancies. In fact, evidence suggests that most of this protective effect is attributable to the first three pregnancies[38].

The current mainstream view is that the cessation of ovulation during pregnancy and breastfeeding inhibits the division and proliferation of ovarian epithelial cells, thereby reducing the chance of initiating or promoting carcinogenesis[39]. A pooled analysis of 13 case-control studies from the Ovarian Cancer Association Consortium showed that breastfeeding can reduce the risk of invasive ovarian cancer by 24% with the greatest reduction observed in high-grade serous ovarian cancer. The duration of breastfeeding can further reduce the risk of ovarian cancer[39]. The risk of ovarian cancer can be reduced by approximately 10% for every 12 months of breastfeeding (RR, 0.89; 95% CI, 0.84–0.94)[20].

Dietary and metabolic factors

Inflammation is a normal physiologic process but long-term, persistent chronic inflammation may promote carcinogenesis by damaging important cell components, activating tumor-promoting signaling pathways, promoting abnormal proliferation, and inhibiting apoptosis[40]. Pro-inflammatory diets have

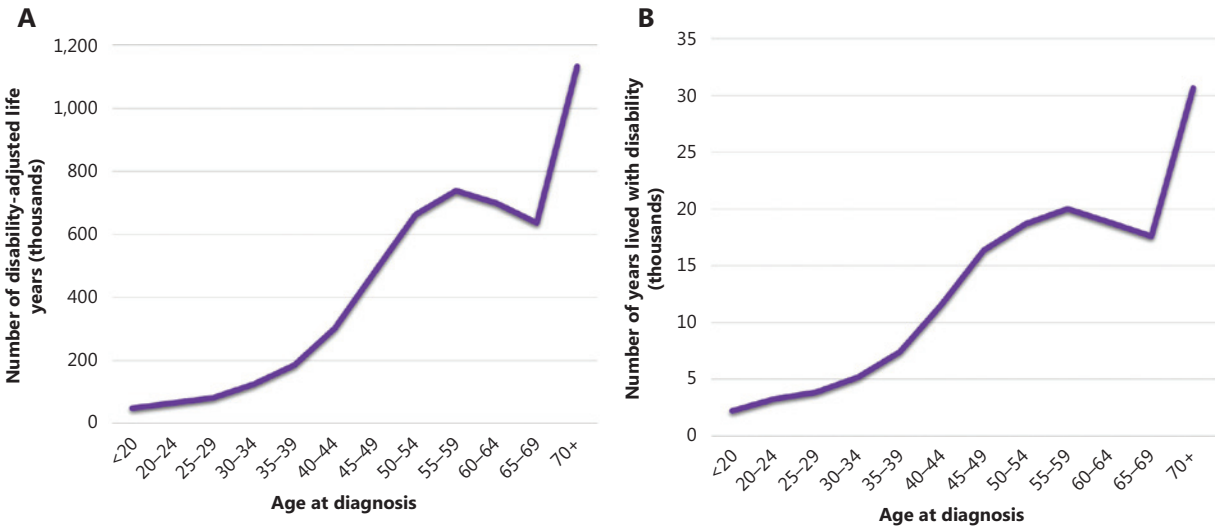


Figure 3 Age-specific disability-adjusted life years (DALYs) and years lived with disability (YLDs) for ovarian cancer in 2021. This figure depicts the distribution of the ovarian cancer disease burden across different age groups in 2021. The x-axis represents the age groups at the time of diagnosis. The y-axis represents the DALYs (A) or YLDs counts (B).

Table 3 Factors associated with the risk of ovarian cancer

Factors	RR, OR, HR, SMR and 95% CI	Reference
Reproductive factor		
Childbirth	Each of the first three pregnancies in ovarian cancer risk [RR, 0.94; 95% CI, 0.92–0.96] Each of the first three pregnancies in clear cell ovarian cancer risk [RR, 0.75; 95% CI, 0.65–0.85]	20
Breastfeeding	Every 12 months of breastfeeding [RR, 0.89; 95% CI, 0.84–0.94]	
Dietary factors		
Vegetable intake	Green leafy vegetables [RR, 0.91; 95% CI, 0.85–0.98] Allium vegetables [RR, 0.79; 95% CI, 0.64–0.96]	21
Fiber intake	Fiber [RR, 0.89; 95% CI, 0.81–0.98]	
Fat intake	Total fat [RR, 1.10; 95% CI, 1.02–1.18] Saturated fat [RR, 1.11; 95% CI, 1.01–1.22] Saturated fatty acid [RR, 1.19; 95% CI, 1.04–1.36] Cholesterol [RR, 1.13; 95% CI, 1.04–1.22]	
Tea intake	Green tea [RR, 0.61; 95% CI, 0.49–0.76]	22
Pro-inflammatory diets	Higher DII scores [OR, 1.42; 95% CI. 1.19–1.65] Each increase in DII point [OR, 1.10; 95% CI, 1.06–1.14]	23
Metabolic factors		
High BMI	Serous borderline ovarian tumor [OR, 1.24; 95% CI, 1.18–1.30] Endometrioid ovarian cancer [OR, 1.17; 95% CI, 1.11–1.23] Mucinous ovarian cancer [OR, 1.19; 95% CI, 1.06–1.32]	24
Diabetes	Diabetes [RR, 1.32; 95% CI, 1.14–1.52]	25

Table 3 Continued

Factors	RR, OR, HR, SMR and 95% CI	Reference
Behavioral factor		
Prolonged sitting time	10–19 h/week sitting [HR, 1.25; 95% CI, 1.04–1.51] ≥ 20 h/week sitting [HR, 1.40; 95% CI, 1.14–1.71]	26
Psychosocial stress	HR, 1.71; 95% CI, 1.16–2.52	27
Medical factors		
Oral contraceptives	Ever *vs.* never [OR, 0.73; 95% CI, 0.70–0.76] Each 5 years of use decreased risk by 20% (95% CI, 18–23%)	28
Hormone replacement therapy	Serous ovarian cancer [RR, 1.53; 95% CI, 1.40–1.66] Endometrioid ovarian cancer [RR, 1.42; 95% CI, 1.20–1.67]	29
Endometriosis	Clear cell ovarian cancer [OR, 3.05; 95% CI, 2.43–3.84] Endometrioid ovarian cancer [OR, 2.04; 95% CI, 1.67–2.48]	30
Pelvic inflammatory disease	Borderline ovarian tumor [OR, 1.50; 95% CI, 1.08–2.08]	31
	Serous borderline ovarian tumor [OR, 1.76; 95% CI, 1.36–2.29]	32
Salpingectomy	Unilateral or bilateral salpingectomy [HR, 0.65; 95% CI, 0.52–0.81] Unilateral salpingectomy [HR, 0.71; 95% CI, 0.56–0.91] Bilateral salpingectomy [HR, 0.35; 95% CI, 0.17–0.73]	33
Genetic factors		
BRCA mutations	BRCA1 carriers (by 70 years of age): 59% (95% CI, 43–76%) BRCA2 carriers (by 70 years of age): 16.5% (95% CI, 7.5–34%)	34
Lynch syndrome	Lifetime risk of 6.7% (95% CI, 5.3–9.1%)	35
Environmental factors		
Occupational asbestos exposure	Standardized mortality ratio, 1.77; 95% CI, 1.3–72.28	36

RR, relative risk; 95% CI, 95% confidence interval; HR, hazard ratio; DII, dietary inflammatory index; OR, odds ratio. The risk factors listed above were associated with overall ovarian cancer when no specific histologic type was specified.

been shown to be a risk factor for ovarian cancer in multiple case-control studies[41,42]. Indeed, there was a positive correlation between dietary inflammatory potential, as measured by the dietary inflammatory index (DII), and the incidence of ovarian cancer in a meta-analysis of six studies. Individuals with higher DII scores had a 42% increased risk for ovarian cancer [odds ratio (OR), 1.42; 95% CI, 1.19–1.65][23]. A multicenter case-control study from Italy involving 1031 ovarian cancer cases and 2411 non-ovarian-cancer cases suggested that a diabetes risk reduction diet reduces the risk of ovarian cancer[43]. A meta-analysis of 97 cohort studies showed that green vegetable, fiber, and green tea intake reduced the risk of ovarian cancer, while total fat, saturated fat, saturated fatty acids, cholesterol, and retinol intake significantly increased the risk[21,22].

Several studies have shown that overweight and obesity increase the likelihood of developing ovarian cancer[44,45]. Cancer cells often exhibit altered metabolic pathways with increased fatty acid oxidation, glycolysis, and glutaminolysis, which contribute to ovarian cancer growth[46]. Research indicates that overweight or obesity can increase the risk of cancer through multiple pathways, including hyperinsulinemia/insulin resistance and abnormalities in the insulin-like growth factor-I (IGF-I) system and signaling, the biosynthesis and action pathways of sex hormones, subclinical chronic low-grade inflammation, and oxidative stress[47]. A Mendelian study suggested a causal link between obesity and aggressive epithelial ovarian cancer with body mass index (BMI) differentially associated with histologic subtypes of ovarian cancer[48]. A pooled analysis of 15 case-control studies in the Ovarian Cancer Association Consortium, including 13,548 cases and 17,913 controls, suggested that high BMI increases the risk of serous borderline ovarian tumor (OR, 1.24; 95% CI, 1.18–1.30), invasive endometrioid ovarian cancer (OR, 1.17; 95% CI, 1.11–1.23), and invasive mucinous ovarian cancer (OR, 1.19; 95% CI, 1.06–1.32) but not high-grade invasive serous cancer[24].

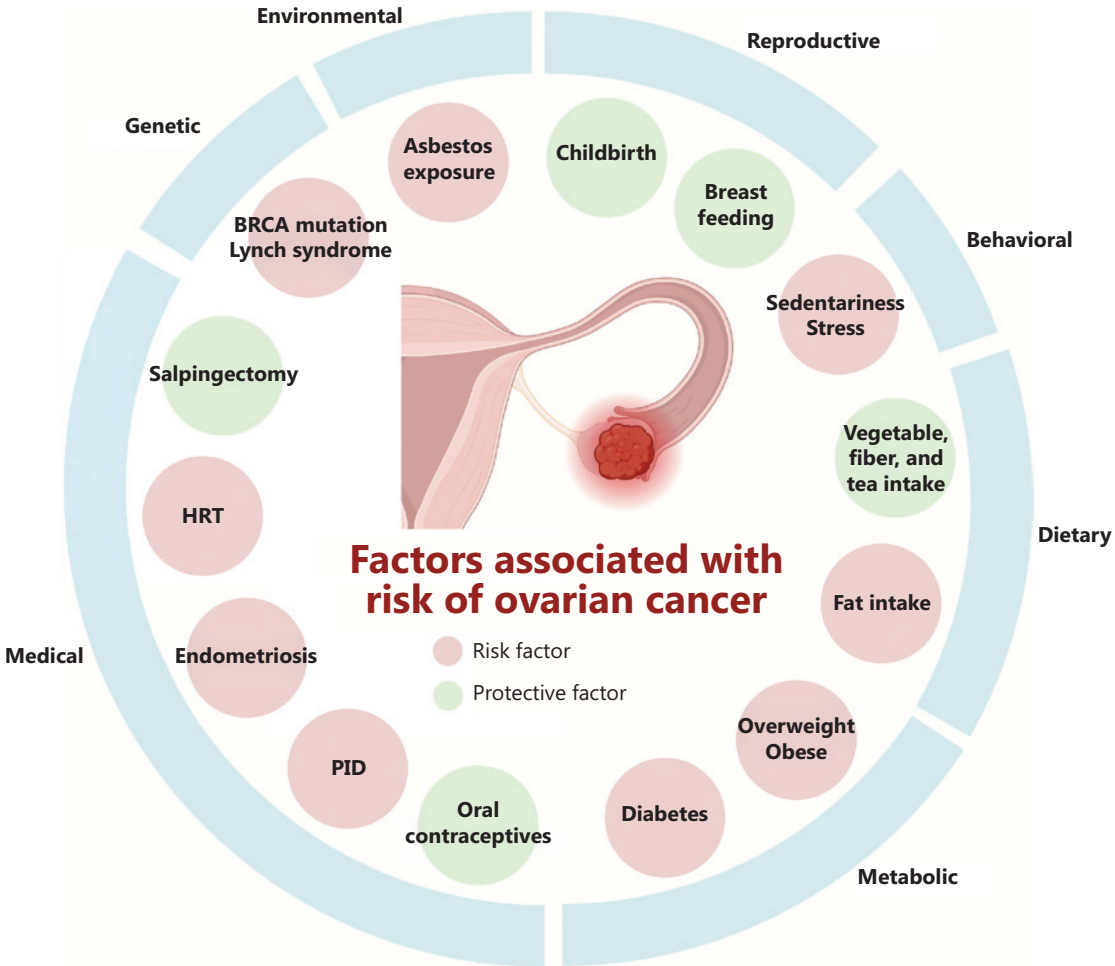


Figure 4 Summary of risk factors for ovarian cancer. This schematic summarizes and categorizes a spectrum of factors linked to ovarian cancer risk, distinguishing between factors that increase risk and factors that confer protection. The factors are organized into seven interconnected categories for systematic understanding, including genetic, reproductive, behavioral, dietary, metabolic, medical, and environmental factors.

Diabetes may also increase the risk of ovarian cancer. Cancer cells rely on aerobic Warburg metabolism to meet the energy needs. Cancer cells also synthesize fatty acids, proteins, and nucleotides. Therefore, cancer cells continuously require an increased supply of glucose and diabetes-related hyperglycemia may fuel this demand[47]. A meta-analysis of 9 case-control and 27 cohort studies suggested that patients with diabetes had a relatively increased risk of ovarian cancer (RR, 1.32; 95% CI, 1.14–1.52)[25] and the association between diabetes and ovarian cancer is more significant in Asian populations[49].

Lifestyle and psychological factors

Prolonged sitting time may increase the risk of ovarian cancer[50]. In a cohort study involving 173,688 participants, women who sat for 10–19 h/week [hazard ratio (HR), 1.25; 95% CI, 1.04–1.51] and women who sat for ≥ 20 h/week (HR, 1.40; 95% CI, 1.14–1.71) had an increased risk compared to women who sat for < 5 h/week[26]. Another meta-analysis involving 26 studies showed that women who engaged in regular recreational physical activity had a 30%–60% lower risk of ovarian cancer[51].

Chronic stress is linked to increased ovarian cancer risk. Stress can lead to increased concentrations of adrenaline and norepinephrine, activate β-adrenergic signaling, then participate in the regulation of various cellular processes involved in the occurrence and development of cancer, such as promoting tumor angiogenesis, inducing DNA damage, inhibiting DNA repair, and reducing tumor cell apoptosis[52]. In a study that included 115,694 participants with > 21 years of follow-up, women who experienced ≥ 3 distress-related psychosocial factors had a > 70% increased risk of ovarian cancer compared

to women who had < 3 distress-related psychosocial factors (HR, 1.71; 95% CI, 1.16–2.52). Notably, when post-traumatic stress disorder was included, the association between distress-related factors and ovarian cancer was strengthened[27].

Medical history

Oral contraceptives have long been known to reduce the incidence of ovarian cancer by inhibiting the ovulation process. Ovulation causes repeated microtrauma to the ovarian epithelial surface, which increases the risk of malignant transformation. This process may explain why oral contraceptives reduce the risk of ovarian cancer[45], especially in women with endometriosis[53]. A Meta-analysis involving 23,257 women with ovarian cancer and 87,303 women without ovarian cancer from 45 studies in 21 countries showed that oral contraceptives can prevent ovarian cancer in the long term (RR, 0.73; 95% CI, 0.70–0.76); the duration of oral contraceptive usage and the reduction in risk displayed a dose-response relationship[28]. However, the protective effect of oral contraceptives may decrease with age or after discontinuation.

Hormone replacement therapy (HRT), which has been widely used to treat menopausal symptoms in women, is associated with an increased risk of ovarian cancer. The main HRT regimens include estrogen alone [estrogen replacement therapy (ERT)] or an estrogen and progestin combination [estrogen-progestin replacement therapy (EPRT)]. The relationship between HRT and the risk of ovarian cancer has not been consistent across studies. A meta-analysis of 52 epidemiologic studies conducted since 1970 showed that for every 1000 women who received hormone therapy for 5 years starting at approximately 50 years of age, 1 additional ovarian cancer patient would be diagnosed. The increase was most pronounced for serous (RR, 1.53; 95% CI, 1.40–1.66) and endometrioid ovarian cancer (RR, 1.42; 95% CI, 1.20–1.67)[29]. Studies have shown a significant correlation between the use of ERT and the incidence of ovarian cancer, while the use of EPRT alone did not increase the risk[54]. This finding may be explained by the fact that most ovarian tumors are estrogen receptor-positive and progesterone may counteract the proliferative effect of estrogen by promoting ovarian cell apoptosis[45]. A meta-analysis of 21 cohort studies showed that the use of HRT increased the risk of ovarian cancer. However, when the research time frame was limited to the past decade, the associated risk was minimal, indicating that the impact of HRT on the incidence of ovarian cancer is not durable[55].

Endometriosis is a recognized risk for ovarian cancer that shares overlapping genetic susceptibility with endometrioid and clear cell subtypes[56]. A large international case-control study including 13,226 controls and 7911 invasive ovarian cancer cases showed that endometriosis was most strongly associated with clear cell carcinoma (OR, 3.05; 95% CI, 2.43–3.84) and endometrioid carcinoma (OR, 2.04; 95% CI, 1.67–2.48)[30]. In like manner, a cohort study involving 450,906 women (78,476 with endometriosis and 372,430 without) showed that women with endometriosis had a higher risk of type I ovarian cancer than women without endometriosis, especially patients with deep infiltrating endometriosis or ovarian endometriotic cysts[53].

Inflammation has been linked to ovarian cancer. In a population-based case-control study including 554 Danish women with invasive ovarian cancer, pelvic inflammatory disease (PID) was associated with increased risk of borderline ovarian tumor (OR, 1.50; 95% CI, 1.08–2.08)[31]. A Swedish case-control study, including 4782 cases and 45,167 controls also reported an elevated risk of serous borderline ovarian tumor among women with a history of PID (OR, 1.76; 95% CI, 1.36–2.29)[32].

Current evidence suggests that high-grade serous ovarian cancer originates from the distal fallopian tube epithelium, forming serous tubal intraepithelial carcinoma that can shed and implant on the ovarian surface[57]. Women who underwent unilateral or bilateral salpingectomy in a population-based cohort study spanning from 1973–2009 in Sweden (n = 34,433) had a significantly lower risk of ovarian cancer compared to women who had not undergone unilateral or bilateral salpingectomy [n = 5,449,119] (HR, 0.65; 95% CI, 0.52–0.81). The reduction in ovarian cancer risk was greater with bilateral salpingectomy than with unilateral[33]. Given the long study period, potential variations in diagnostic criteria, surgical practices, and classification systems should be considered. For example, changes in Swedish surgical coding after 1997 prevented distinction between unilateral and bilateral salpingectomy, which limited stratified analyses. Nevertheless, because meaningful risk reduction typically emerges >10 years after salpingectomy, the extended follow-up and large sample size still lend substantial strength to these findings. Evidence linking hysterectomy to the risk of ovarian cancer remains inconsistent. Several studies have found no significant association between hysterectomy for benign gynecologic conditions and ovarian cancer incidence[58,59], whereas other studies have reported a modest reduction in risk[60].

Genetic factors

Hereditary breast-ovarian cancer syndrome is a major genetic predisposition to ovarian cancer. Hereditary breast-ovarian cancer syndrome results primarily from pathogenic variants (mutations) in the *BRCA1* or *BRCA2* genes, which have key roles in DNA damage repair[61]. *BRCA1* and *BRCA2* gene mutations are associated with a high lifetime risk of ovarian cancer. It is estimated that by 70 years of age, the average cumulative risk of ovarian cancer for *BRCA1* mutation carriers is 41% and 15% for *BRCA2* mutation carriers[62].

Lynch syndrome also contributes to hereditary ovarian cancer. Lynch syndrome is an autosomal dominant disorder caused by germline pathogenic variants in DNA mismatch

repair (*MMR*) genes. Women with a family history of Lynch syndrome have a 6.7% lifetime risk of ovarian cancer[35]. The increased risk of ovarian cancer in Lynch syndrome is not histology-specific. In contrast, high-grade serous carcinoma is nearly the only histologic type of hereditary ovarian cancer in hereditary breast-ovarian cancer syndrome with *BRCA* mutations, suggesting that hereditary breast-ovarian cancer may have a different nature from ovarian cancer in Lynch syndrome[63].

Environmental and occupational exposures

Some occupational and environmental exposures may increase ovarian cancer risk. A meta-analysis of 18 cohort studies involving women with occupational asbestos exposure showed that asbestos exposure was associated with an increased risk of ovarian cancer (standardized mortality ratio, 1.77; 95% CI, 1.37–2.28)[36]. Talc, which is structurally similar to asbestos, was among the first environmental risk factors identified for ovarian cancer. Earlier studies suggested that talc use increases the risk of ovarian tumors, especially serous subtypes[64]. However, recent evidence remains inconsistent. Case-control studies often report a weak positive association, whereas cohort studies consistently showed null results, with the discrepancy likely due to recall bias or residual confounding[65-67].

Racial and ethnic disparities

Ovarian cancer risk and outcomes differ across racial and ethnic groups and are influenced by underlying social determinants, such as socioeconomic status (SES) and access to healthcare. Data from the US Centers for Disease Control and Prevention indicated that ovarian cancer rates are the highest among non-Hispanic American Indian, native Alaskan, and non-Hispanic White women, while the rates are low among Hispanic, non-Hispanic Asian and Pacific Islander, and non-Hispanic Black women. The higher rates among non-Hispanic White women may be due to the higher incidence of hereditary breast and ovarian cancer mutations in the Ashkenazi Jewish population[68]. SES can influence the risk and prognosis of ovarian cancer through multiple pathways. Women from lower-SES backgrounds are more likely to experience adverse lifestyle and metabolic factors, such as obesity and chronic inflammation, and to have lower utilization of preventive healthcare services, all of which may increase ovarian cancer risk[69]. Limited access to gynecologic care, delay in diagnosis, and decreased adherence to guideline-recommended treatment have also been associated with a higher likelihood of presenting with advanced-stage ovarian cancer and poorer survival outcomes[70]. Furthermore, a meta-analysis demonstrated marked disparities in treatment adherence and mortality across racial and socioeconomic groups. Black patients had a 25% lower rate of adherence to ovarian cancer treatment (RR, 0.75; 95% CI, 0.66–0.84) and an 18% higher risk of mortality (RR, 1.18; 95% CI, 1.11–1.26) compared to White patients. Patients in the lowest SES category had a 15% lower adherence rate compared to patients in the highest SES group (RR, 0.85; 95% CI, 0.77–0.94) and individuals with fewer hospital visits showed a 30% lower adherence rate compared to patients with more frequent healthcare contact (RR, 0.70; 95% CI, 0.58–0.85)[71].

Screening of ovarian cancer

In ovarian cancer screening women are divided into average- and high-risk populations. Women with a family history of cancer or carrying *BRCA1*, *BRCA2*, or other pathogenic variants have an increased ≥ 10% lifetime risk of ovarian cancer compared to women with an average risk[72,73]. Because patients with early-stage ovarian cancer frequently lack symptoms, screening and early detection remain challenging.

Clinical trials, such as SCSOCS (82,487 participants with a mean follow-up of 9.2 years) and PLCO (78,216 participants with a mean follow-up of 12.4 years), demonstrated that screening strategies using serum CA-125 combined with transvaginal ultrasound did not result in downstaging or a reduction in ovarian cancer mortality for women at average risk[74]. The UKCTOCS trial, which involved 202,638 participants with a median follow-up of 16.3 years, reported that a multimodal screening strategy consisting of longitudinal serum CA-125 levels interpreted by the risk of ovarian cancer algorithm (ROCA) calculation combined with transvaginal ultrasound findings, down-staged ovarian cancer but did not reduce ovarian cancer mortality[75]. Therefore, screening is not recommended for average-risk individuals according to the international guidelines from the National Comprehensive Cancer Network, the European Society of Medical Oncology, and the Society of Gynaecological Oncology and Ovarian Cancer Alliance[76,77].

A GOG trial involving 3692 high-risk women with a strong family history of *BRCA1/2* pathogenic variants and a median follow-up of 6 years showed that ROCA-based multimodal screening every 3 months had better sensitivity and high specificity for early-stage ovarian cancer[23]. The UKFOCSS trial recruited 4348 high-risk women (≥ 10% lifetime risk) and performed ROCA-based multimodal screening every 4 months. This strategy resulted in downstaging of ovarian cancer after a median follow-up of 4.8 years. However, the impact on mortality could not be evaluated[42]. A serum CA-125 level and transvaginal ultrasound screening findings remain an option with uncertain benefit for high-risk women who wish to delay or decline risk-reducing surgery[76,77].

Artificial intelligence (AI)-enabled screening has recently emerged as a potential approach for early detection of ovarian cancer. Research involving 10,992 individuals (1 internal validation set of 3007 individuals and 2 external validation sets of 7985 individuals) from China used an AI model to interpret laboratory tests, achieved an area under the receiver-operating characteristic curve (AUC) of 0.949 in the internal validation set and an AUC of 0.88 in the external validation sets[78]. Another deep learning model using 17,119 ultrasound images from 3652 patients across 20 centers in 8 countries also reported promising diagnostic accuracy in detecting ovarian cancer[79]. The integration of AI into ovarian cancer screening offers a promising approach for improving early detection by uncovering complex, non-linear relationships within multi-modal datasets that may elude traditional analysis. However, this potential is limited by significant challenges, including the "black-box" nature of many algorithms, which can obscure the reasoning underlying decisions. Rigorous external validation and prospective clinical trials are also necessary to demonstrate a tangible impact on patient outcomes, such as down-staging or reduced ovarian cancer mortality.

Several novel biomarkers and screening strategies are under investigation, including DNA methylation biomarkers[80], circulating tumor (ct) DNA[81], glycosylated CA-125[82], and other candidate biomarkers, such as Osteopontin, Human Epididymis Protein 4, and so on[83]. Targeted cell-free DNA methylation analysis had sensitivities for ovarian cancer of 83.1% (95% CI, 72.2–90.3%) across all stages and 50% (95% CI, 23.7–76.3%) in stage I based on the Circulating Cell-free Genome Atlas (CCGA) study[84]. Whether these new methods can achieve down-staging or reduce ovarian cancer mortality requires further investigation.

Prevention of ovarian cancer

Although ovarian cancer screening has limited efficacy, both non-surgical and surgical options are available to reduce ovarian cancer risk.

Non-surgical prevention is primarily achieved through use of oral contraceptives[12]. Oral contraceptive use is associated with a 40%–50% reduction in lifetime ovarian cancer risk among women at average risk[85]. Women carrying *BRCA1* or *BRCA2* mutations are also advised to consider oral contraceptive use for prevention[86]. A longer duration of oral contraceptive use provides greater protection for average- and high-risk populations, although the potential risk of thrombosis should be considered[87,88]. The levonorgestrel intrauterine device (LNG-IUD) has also been shown to reduce ovarian cancer risk in women at average risk for ovarian cancer[89,90].

Risk-reducing salpingo-oophorectomy (RRSO) can reduce ovarian cancer risk by 80%–97% in *BRCA* carriers and reduce the mortality rate. Therefore, for high-risk individuals who have completed childbearing, bilateral RRSO is recommended for pre-menopausal women with a ≥ 4% lifetime risk of ovarian cancer and post-menopausal women with a ≥ 5% lifetime risk of ovarian cancer[72,91]. *BRCA1* mutation carriers are advised to undergo RRSO between 35 and 40 years of age, *BRCA2* carriers between 40 and 45 years of age, and *RAD51C*, *RAD51D*, *PALB2*, and *BRIP1* carriers ≥ 45 years of age[92]. The timing of RRSO may be individualized based on family history and personal choices[86]. HRT is recommended for pre-menopausal women following RRSO if they do not have a personal history of breast cancer[93,94].

Risk-reducing salpingectomy with or without delayed oophorectomy (RRSDO) represents an alternative for premenopausal women who wish to retain ovarian function[72,86]. The multicenter non-randomized controlled TUBA study recruited 577 women with a *BRCA1/2* pathogenic variant from the Netherlands and showed that women undergoing RRSDO reported a better menopause-related quality of life than women who underwent RRSO[95]. The USWISP study used a similar design in 190 women and reported that the RRSO group exhibited worsening menopausal symptoms and greater decision regret[96]. The long-term safety and prophylactic effect of RRSDO are under evaluation. The ongoing TUBA-WISP II trial aims to determine whether delayed oophorectomy after salpingectomy is non-inferior to immediate RRSO in reducing tubo-ovarian cancer risk. However, follow-up remains too short for conclusions[97]. To date, RRSO remains the gold standard for risk reduction[98].

RRSO should not be undertaken for ovarian cancer prevention in women at average risk. Opportunistic bilateral salpingectomy (OBS) may be offered at the time of benign gynecologic surgery, after childbearing, and following counselling on benefits and risks with informed consent[72,91].

Endometriosis management should also be considered with respect to endometriosis-associated ovarian cancer. Medical or surgical treatment should be individualized according to age, reproductive plans, and disease characteristics[99].

Therapeutic landscape

Although each subtype of ovarian cancer has various clinical features, molecular characteristics, and different prognoses, the subtypes share a similar principle of treatment. Complete cytoreduction (R0 resection) remains the cornerstone of ovarian cancer treatment across disease stages and settings, including primary, interval, and secondary cytoreductive surgery[100,101]. Platinum-based combination chemotherapy remains the standard first-line regimen for most histologic subtypes of ovarian cancer. The introduction of targeted therapy has transformed management paradigms. Bevacizumab, a monoclonal antibody targeting VEGF, is recommended in combination with cytotoxic chemotherapy for stage II–IV disease, followed by maintenance therapy (ICON7

and GOG-218)[102,103]. However, neither trial showed a significant overall survival benefit in the entire population. Further analysis in ICON-7 demonstrated that the high-risk subgroup, defined by stage IV ovarian cancer, inoperable stage III disease, or sub-optimally debulked (> 1 cm) stage III disease, received a significant overall survival benefit from bevacizumab administration with an HR of 0.78 (0.63–0.97). The analysis suggested that residual tumor burden, presumably producing VEGF, is necessary to enable bevacizumab to exert an effect on the tumor microenvironment.

Poly (ADP-ribose) polymerase (PARP) inhibitors represent a major therapeutic advance. Maintenance therapy with olaparib or niraparib, with or without bevacizumab, substantially prolongs progression-free and overall survival in patients with germline *BRCA1/2* mutations or homologous recombination deficiency (HRD) [104-106]. In contrast, benefits in non-*BRCA* and HRD-proficient patients remain limited. Results from immunotherapy trials have been largely disappointing[107], which can be attributed to tumor heterogeneity as well as inherent or acquired immunotherapy resistance associated with the tumor microenvironment. However, recent combination regimens have shown promise. The DUO-O trial demonstrated that non-*BRCA*-mutated patients receiving chemotherapy, bevacizumab, durvalumab, and olaparib achieved a median progression-free survival (PFS) of 24.2 months (HR, 0.63 *vs.* control)[108]. The KEYLYNK-001 trial reported an improved PFS (22.2 months; HR, 0.71) with chemotherapy plus pembrolizumab followed by olaparib maintenance[109]. Further biomarker development is required to enable more personalized therapeutic strategies.

Conclusions and future perspectives

The interpretation of global epidemiology is subject to heterogeneity in the methodologies and quality of the underlying cancer registries. Although the incidence of ovarian cancer has declined in some high-income countries, an upward trend persists in other countries. Globally, mortality has decreased, but despite advances in targeted therapy and other modalities, improvements in overall survival remain limited. Further exploration of underlying mechanisms is warranted. Modifying lifestyle and reproductive factors offers a feasible approach to reduce ovarian cancer risk. Women should be educated on the impact of reproductive decisions, physical activity, and diet on their future cancer risk. RRSO remains the most effective preventive measure for high-risk women. Public health policies should focus on promoting awareness, managing modifiable risk factors, and facilitating access to preventive surgery.

Future epidemiologic research should explore novel determinants to refine the understanding of ovarian cancer etiology. Large-scale multicenter cohort studies are needed to evaluate emerging factors, such as metabolomic signatures, gut microbiota composition, and chronic inflammatory states. The next frontier lies in the development of improved early detection strategies, in which AI and molecular biomarkers are potentially poised to play a role.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

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