Epidemiology and Etiology of Ovarian Cancer

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Abstract

The median age of patients diagnosed with ovarian cancer is 63 years in the United States, and the risk for developing this cancer increases with age. The age-adjusted incidence rate of ovarian cancer is 11.9 per 100,000 females, which is relatively low, and it ranks 17th among all cancers. On the other hand, the mortality from this cancer is relatively high, and the age-adjusted mortality is 7.5 per 100,000 females. Both the annual incidence rate and the mortality have been declining in recent years, reflecting advances in treatment. From a global viewpoint, the incidence rate is higher in developed countries (especially in Northern Europe) compared to developing countries.

Although the cause of ovarian cancer is still unknown, several risk factors related to its development have been identified. The most important factors are the family history and genetic background, which account for approximately 10% of ovarian cancer. Hereditary breast and ovarian cancer and Lynch syndrome are associated with mutations of certain genes. Other causes of ovarian cancer that have been suggested include continuous ovulation, excessive gonadotropin stimulation, excessive hormone stimulation, and pelvic inflammation. Ovarian cancer occurs more frequently among nulliparous women and infertile women, while it is less frequent among women with a history of oral contraceptive use, pregnancy, or breastfeeding.

Keywords

Ovarian cancer • Incidence rate • Mortality • Risk factor

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1.1 Introduction

Ovarian cancer is uncommon and often advanced at the time of diagnosis and has a poor prognosis. The prevalence of ovarian cancer is influenced by the social background, demographic factors, racial and ethnic factors, and lifestyle factors. The survival rate of ovarian cancer patients has improved with the development and standardization of new treatments. It is important to be aware of epidemiological trends in the diagnosis and treatment of ovarian cancer. This section provides an outline of the age distribution of ovarian cancer, annual changes of the incidence rate and mortality, and international comparisons, as well as information about epidemiology and etiology with a focus on risk factors.

1.2 General Epidemiology of Ovarian Cancer

Ovarian cancer includes various tumors that arise from the ovaries, and its histological classification is based on the classification of the World Health Organization (WHO) [1]. Superficial epithelial/stromal tumors account for approximately 80% of all ovarian tumors. These tumors contain epithelial and interstitial tissues in various proportions, and the tumor components are normally derived from the epidermis. Sex cord-stromal tumors are derived from granulosa cells and Sertoli cells, theca cells differentiating from the interstitium, or Leydig cells and account for approximately 5% of all ovarian tumors. Germ cell tumors are derived from germ cells or extraembryonic tissues and comprise approximately 15–20% of all ovarian tumors. Although ovarian cancer occurs in all age groups, the histological types vary with age (Table 1.1) [2]. While malignant germ cell tumors are most frequent in young women aged 20 years or younger, malignant epithelial tumors are frequent in older women aged 50 years or older.

Some patients with ovarian cancer have a positive family history or genetic background, and the disease is called familial ovarian cancer in a broad sense if a patient has a relative with ovarian cancer. If a patient has a family history of ovarian cancer in close relatives or a number of relatives with this cancer, it is called familial or hereditary ovarian cancer, including hereditary breast and ovarian cancer (HBOC) and Lynch syndrome. Hereditary ovarian cancer is estimated to account for approximately 10% of all ovarian cancer [3, 4].

Globally, it has been reported that approximately 200,000 women are diagnosed with ovarian cancer and 125,000 women die of this cancer every year [5, 6].

Table 1.1 Primary ovarian neoplasms related to age (From ref. 2)

Type	<20 years	20–50 years	>50 years
Coelomic epithelium	29%	71%	81%
Germ cell	59%	14%	6%
Specialized gonadal stroma	8%	5%	4%
Non-specific mesenchyme	4%	10%	9%

1.3 Current Status and Changes of Ovarian Cancer Incidence Rate

The "number of cases (or number of deaths)" is the "number of cases (or deaths) newly diagnosed during a certain period (usually 1 year) in a target population," and it is often expressed as the "incidence rate (mortality)." However, in diseases such as cancer for which age is considered to be a contributing factor, the age-stratified incidence rate (or mortality) is important, and therefore the "age-specific incidence rate (or mortality)" is calculated. When comparing incidence rate (or mortality) between different regions or periods, it is difficult to perform accurate comparison due to differences in the age distribution of the target populations. To overcome this problem, the "age-adjusted incidence rate (or mortality)" is often calculated, which is the incidence rate (or mortality) adjusted for the age-specific population of the standard population, in order for the age composition to be the same as that of the standard population.

The detailed trends of cancer prevalence and mortality are reported by the Surveillance, Epidemiology, and End Results (SEER) program compiled by the National Cancer Institute (NCI) in the United States [7]. Although SEER is based on data from the United States, it can be used as a relatively general reference since the racial composition of the population is diverse in the United States.

According to the 2009–2013 data, the age-adjusted incidence rate of ovarian cancer is 11.9 per 100,000 females. According to the 2010–2012 data, the lifetime risk of ovarian cancer for women is 1.3% (approximately 1 out of every 78 females). The population of women in the United States is approximately 160 million (2015 data) [8], and the estimated annual number of patients developing ovarian cancer in the United States is 22,280 (as of 2016), while it is estimated that there were a total of 195,767 patients with ovarian cancer in 2013. The cancer causing the highest age-adjusted incidence rate for women is breast cancer, and the incidence rate is 125.0 per 100,000 females. The incidence rate due to ovarian cancer is less than one tenth of that caused by breast cancer, and it is ranked 17th among all cancers affecting women in terms of the estimated annual number of patients, accounting for only 1.3% of new cancers annually (Table 1.2).

Table 1.2 Estimated new cases and deaths compared to other cancers: ovarian cancer (From ref. 7)

Common types of cancer	Estimated new cases 2016	Estimated deaths 2016
1 Breast cancer (female)	246,660	40,450
2 Lung and bronchus cancer	224,390	158,080
3 Prostate cancer	180,890	26,120
4 Colon and rectum cancer	134,490	49,190
5 Bladder cancer	76,960	16,390
6 Melanoma of the skin	76,380	10,130
7 Non-Hodgkin lymphoma	72,580	20,150
8 Thyroid cancer	64,300	1,980
9 Kidney and renal pelvis cancer	62,700	14,240
10 Leukemia	60,140	24,400
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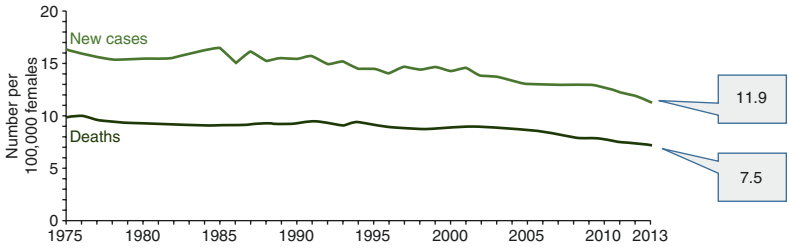
17 Ovarian cancer	22,280	14,240



Year	1975	1980	1985	1990	1995	2000	2004	2008
5–Year relative survival	33.7%	38.2%	38.7%	40.4%	42.2%	43.0%	44.3%	46.2%

1975–2013, All races, females. Rates are age-adjusted.

Fig. 1.1 Trends of age-adjusted incidence rate, mortality, and 5-year relative survival rate: ovarian cancer (From ref. 7)

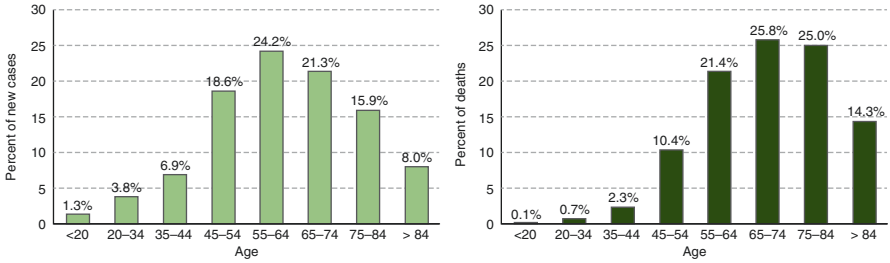


Fig. 1.2 Percentage of new cases and deaths by age group: ovarian cancer (From ref. 7)

Thus, ovarian cancer is relatively infrequently in proportion to all cancers. The annual age-adjusted incidence rate of ovarian cancer has been decreasing, as it was 16.3 per 100,000 females in 1975, 15.4 in 1990, 13.0 in 2005, and 11.9 in 2013 (Fig. 1.1).

The median age of women diagnosed with ovarian cancer is 63 years. As for the age-specific incidence, 1.3% of women with ovarian cancer are diagnosed at 19 years or younger, 3.8% at 20–34 years, 6.9% at 35–44 years, 18.6% at 45–54 years, 24.2% at 55–64 years, 21.3% at 65–74 years, 15.9% at 75–84 years, and 8.0% at 85 years or older (Fig. 1.2). Thus, the prevalence of ovarian cancer increases with age, and it increases rapidly from the age of 45 years. Patients who are 45 or older comprise 88% of the total number of patients, with a peak at 55–64 years. These points suggest that aging is an important factor in the development of ovarian cancer.

As for racial/ethnic background, the age-adjusted incidence rate per 100,000 females is 12.5 for whites, 9.6 for blacks, 9.3 for Asian/Pacific islanders, 10.4 for American Indians/Alaskan natives, 10.6 for Hispanics, and 12.0 for non-Hispanics. Thus, ovarian cancer incidence rate tends to be lower among blacks and Asians, while it is higher among whites and non-Hispanics (Fig. 1.3).

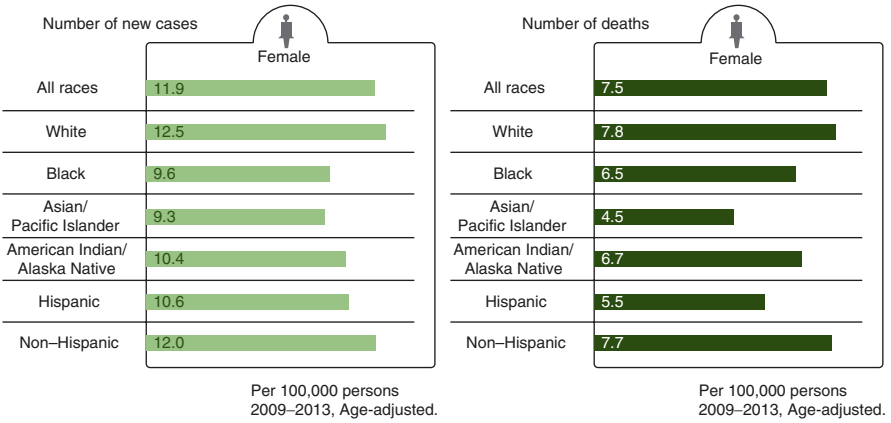


Fig. 1.3 Age-adjusted incidence rate and mortality by race/ethnicity: ovarian cancer (From ref. 7)

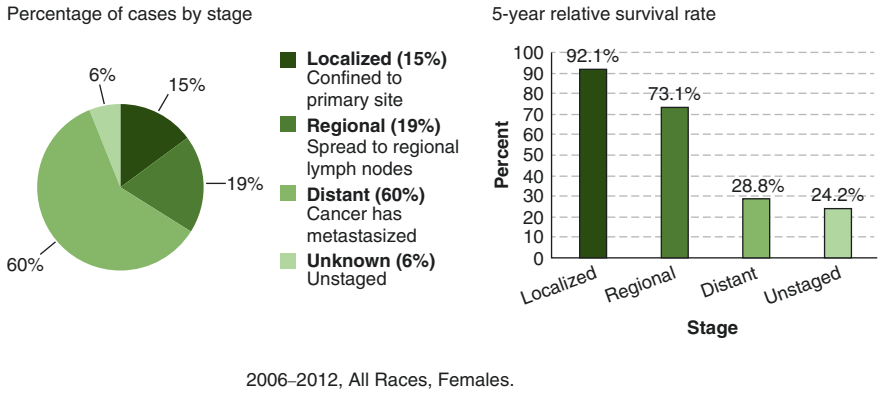


Fig. 1.4 Percentage of cases and 5-year relative survival rate by stage at diagnosis: ovarian cancer (From ref. 7)

Ovarian cancer is confined to the ovary at diagnosis in 15% of patients, while it has spread to regional lymph nodes in 19% and has spread or metastasized beyond the primary site in 60% (the details are unknown in 6%), indicating that more than half of all patients have advanced disease at diagnosis (Fig. 1.4). In older women, ovarian cancer is diagnosed at a relatively more advanced stage than in young women.

On the other hand, the trends of cancer prevalence and mortality in Japan are reported by the Cancer Registry and Statistics in Cancer Information Service, National Cancer Center, Japan [9], and the annual report of the Committee on Gynecologic Oncology, Japan Society of Obstetrics and Gynecology (JSOG) [10]. As of 2012, the age-adjusted incidence rate of ovarian cancer was 8.3 per 100,000 females. That of all sites of female cancer was 265.8 per 100,000 females, and that of breast cancer was 64.3 per 100,000 females, which was the highest in female cancers. Ovarian cancer is ranked seventh among all sites of

female cancers and accounting for 3.1% of new cancers. In Japan, the annual age-adjusted incidence rate of ovarian cancer has doubled in these 30 years. Patients aged 60–69, 50–59, and 40–49 years accounted for 26.9%, 24.6%, and 21.5%, respectively, of all patients whose treatment was initiated in 2013. Women in their 50s and 60s were predominantly affected by ovarian cancer, same as the report on SEER. The distribution of surgical stages is as follows: stage I (confined to primary site) accounted for 42.2%, stage II (spread to pelvic cavity) accounted for 9.8%, stage III (spread to regional lymph nodes and/or peritoneal cavity) accounted for 28.2%, and stage IV (metastasize to distant organs) accounted for 8.3% of all patients. Neoadjuvant chemotherapy was administered to 10.9% of patients.

1.4 Current Status and Changes of Ovarian Cancer Mortality

According to SEER [7], the age-adjusted mortality rate of ovarian cancer was 7.5 per 100,000 females in 2009–2013. Based on the 2006–2012 data, the 5-year survival rate of ovarian cancer patients was 46.2%, indicating that more than half of these patients die within 5 years. In the United States, 14,240 patients are predicted to die of ovarian cancer in 2016 (Table 1.2). Ovarian cancer accounts for 2.4% of all cancer deaths, which is high in proportion to the number of patients with this tumor. When compared to the 5-year survival rate of 89.7% for breast cancer and the 40,450 estimated annual deaths (21.5 per 100,000 females) from this cancer, which has the highest estimated annual incidence, the higher risk of death from ovarian cancer becomes obvious. However, the annual age-adjusted mortality due to ovarian cancer is decreasing, as it was 9.8 per 100,000 females in 1975, 9.3 in 1990, 8.7 in 2004, and 7.5 in 2013. In addition, the 5-year survival rate is increasing, since it was 33.7% in 1975, 40.4% in 1990, and 46.2% in 2008 (Fig. 1.1). This improvement is thought to be due to advances in operative treatment and to the development and standardization of novel chemotherapy regimens.

The median age at which patients die of ovarian cancer is 70 years. As for the age-specific mortality, 0.1% of patients die at 19 years or younger, 0.7% at 20–34 years, 2.3% at 35–44 years, 10.4% at 45–54 years, 21.4% at 55–64 years, 25.8% at 65–74 years, 25.0% at 75–84 years, and 14.3% at 85 years or older (Fig. 1.2). The ovarian cancer mortality is in proportion to the incidence of this cancer and thus increases with age to a peak at 55–64 years.

With respect to the influence of racial/ethnic background, the age-adjusted mortality per 100,000 females is 7.8 for whites, 6.5 for blacks, 4.5 for Asian/Pacific islanders, 6.7 for American Indians/Alaskan natives, 5.5 for Hispanics, and 7.7 for non-Hispanics. Thus, mortality tends to be lower in Asian/Pacific islanders and Hispanics compared with the incidence of this cancer (Fig. 1.3).

The 5-year survival rate at the time of diagnosis of ovarian cancer is 92.1% if the tumor is confined to the ovary, 73.1% if it has spread to regional lymph nodes, 28.8% if it has spread or metastasized beyond the region, and 24.2% when the

details are unknown. Therefore, the prognosis is poorer as the disease becomes more advanced, and the overall prognosis is poor because many patients have advanced disease at the time of diagnosis (Fig. 1.4).

According to the Cancer Registry and Statistics in Japan [9], the age-adjusted mortality rate of ovarian cancer was 3.1 per 100,000 females in 2014. That of all sites of female cancer is 63.0 per 100,000 females, and that of breast cancer is 8.9 per 100,000 females. Ovarian cancer is ranked eighth among all sites of female cancers and accounting for 4.9% of all female cancer deaths. Based on the 2006–2008 data, the 5-year survival rate of ovarian cancer patients was 58.0%. Those in 1993–1996, in 1997–1999, in 2000–2002, and in 2003–2005 are 49.4%, 52.0%, 53.3%, and 55.0%, respectively. The 5-year survival rate also has been gradually improving in Japan. According to the annual report of JSOG for patients whose treatment was initiated in 2008 [10], the 5-year survival rates were 90.5% in stage I patients, 73.3% in stage II patients, 47.8% in stage III patients, and 30.2% in stage IV patients. Patients with serous carcinoma had a significantly poorer prognosis compared with those with mucinous carcinoma, endometrioid carcinoma, and clear cell carcinoma.

1.5 International Comparison of Ovarian Cancer Incidence Rate and Mortality

The International Agency for Research on Cancer (IARC), which is an agency of the World Health Organization (WHO), has reported the trends for the incidence and death from ovarian cancer based on data from 184 countries [11]. As of 2012, the age-adjusted regional ovarian cancer incidence rate is 8.0–9.9 per 100,000 females in Europe, North America, and Oceania versus 4.8–5.6 in Africa, South America, and Asia, being somewhat higher in Western countries (Fig. 1.5). Also as of 2012, the age-adjusted regional ovarian cancer mortality is 4.9–5.4 per 100,000 females in Europe, North America, and Oceania versus 3.0–3.8 in Africa, South America, and Asia, showing a relatively higher number of deaths in South America and Africa compared to the incidence in these regions (Fig. 1.5). The age-adjusted incidence rate in developed countries is 9.1 per 100,000 females, and it is 5.0 per 100,000 females in developing countries, while the age-adjusted mortality is 5.0 and 3.1 per 100,000 females, respectively, suggesting higher incidence rate and mortality from ovarian cancer in developed countries.

When comparing representative countries from each region, including annual changes (Fig. 1.6), ovarian cancer incidence rate is highest in countries from Northern and Eastern Europe (such as Denmark, Norway, and the Czech Republic), followed by Western Europe and North America, but the overall incidence rate tends to be low. While ovarian cancer incidence rate is generally low in Asia and Central or South America, it is increasing in Brazil and Japan. As for ovarian cancer mortality, it is decreasing markedly in Western countries but remains unchanged in other regions where the mortality has previously been lower (Fig. 1.6).

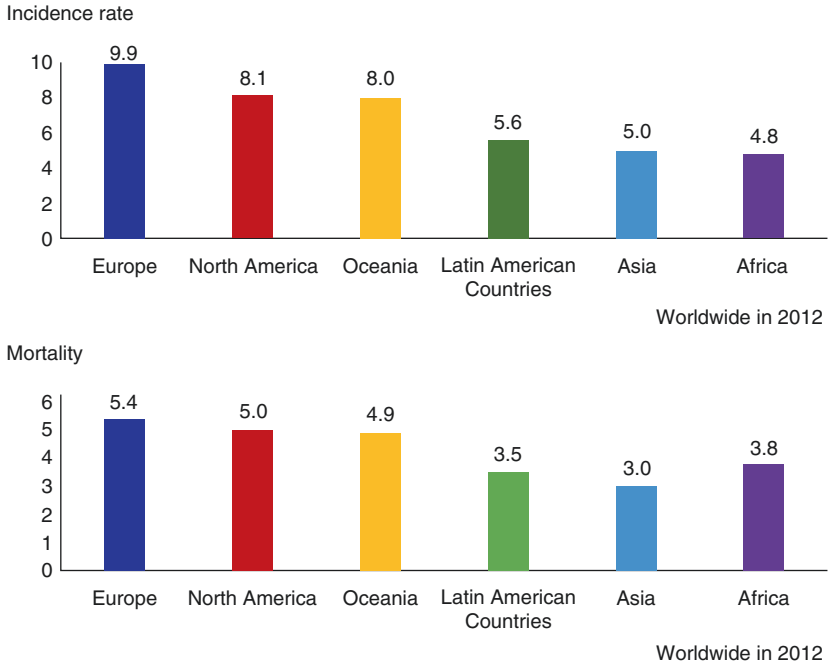


Fig. 1.5 Estimated age-adjusted incidence rate and mortality by regions: ovarian cancer (From ref. 9)

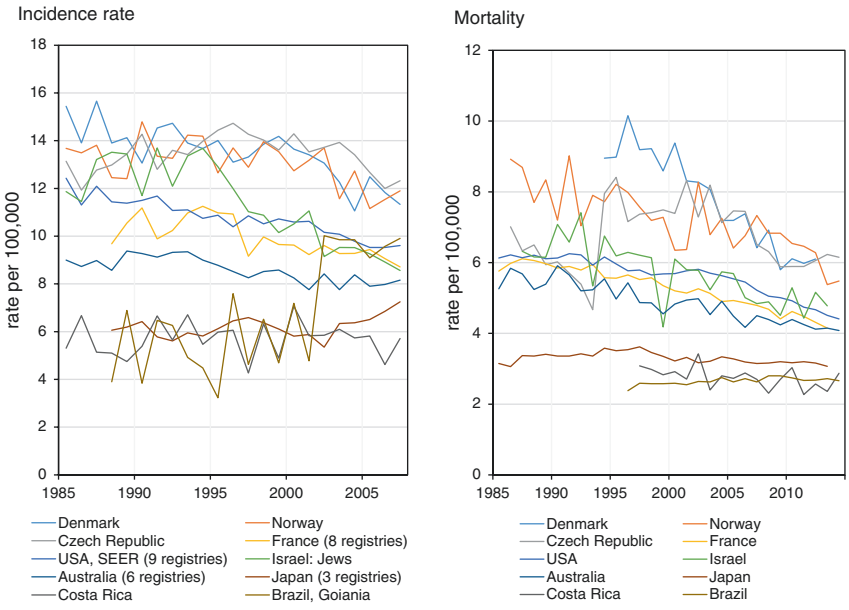


Fig. 1.6 Time trends of age-adjusted incidence rate and mortality: ovarian cancer (From ref. 9)

Although the risk of ovarian cancer is influenced by geographical and racial factors, global differences may become smaller in the future due to environmental factors and population mobility.

1.6 Risk Factors for Ovarian Cancer

The details of the etiology of ovarian cancer are unknown at present, although several environmental, biological, and genetic risk factors have been identified (Table 1.3) [12].

There have been many reports of familial ovarian cancer, and a family history of breast cancer or ovarian cancer is the most important known risk factor for this tumor [13, 14]. In particular, the relative risk is increased by threefold or more for a female who has a first-degree relative with ovarian cancer (e.g., mother, daughter, or sister) [15]. In the case of hereditary ovarian cancer, the influence of cancer-related gene mutations is considered to be significantly stronger than other factors. The characteristic feature of hereditary breast and ovarian cancer (HBOC) is the presence of multiple family members with early-onset breast cancer or ovarian cancer. HBOC is caused by mutation of *BRCA1* or *BRCA2*, which functions as tumor suppressor genes. The lifetime risk of developing ovarian cancer is 30% for women with *BRCA1* mutation and 27% for those with *BRCA2* mutation [16, 17]. Lynch syndrome is characterized by the presence of a family member with early-onset

Table 1.3 Risk factors for epithelial ovarian cancer (From ref. 10)

Increased	Decreased	Indeterminate
Hereditary – Family history of ovarian cancer – Personal history of breast cancer – Alteration in *BRCA1* or *BRCA2* – Lynch syndrome Reproductive – Advanced age – Nulligravida – Infertility Hormonal – Early age at menarche – Late age at natural menopause – Hormone replacement therapy – Estrogen – Androgens Inflammatory – Perineal talc exposure – Endometriosis – Pelvic inflammatory disease Lifestyle – Obesity Geography – Extremes in latitude	Reproductive – Multiparity – Breastfeeding Hormonal – Oral contraceptives – Progestins Surgery – Hysterectomy – Tubal ligation	Fertility drugs Exercise Cigarette smoking

Table 1.4 Factors suggestive of an inherited predisposition to breast and/or ovarian cancer (From ref. 18)

HBOC	– Personal history of both breast and ovarian cancer – Personal history of ovarian cancer and a close relative with breast cancer at ≤50 years or ovarian cancer at any age – History of ovarian cancer at any age combined with Ashkenazi Jewish ancestry – History of breast cancer at ≤50 years and a close relative with ovarian or male breast cancer at any age – Women of Ashkenazi Jewish ancestry and breast cancer at ≤40 years – Women with a first-degree or second-degree relative with a known *BRCA1* or *BRCA2* mutation – Women with bilateral breast cancer (particularly if the first cancer was at ≤50 years) – Women with breast cancer at ≤50 years and a close relative with breast cancer at ≤50 years – Women of Ashkenazi Jewish ancestry with breast cancer at ≤50 years – Women with breast or ovarian cancer at any age and two or more close relatives with breast cancer at any age (particularly if at least one breast cancer was at ≤50 years)
Lynch	– Women with endometrial or colorectal cancer who have At least three relatives with a Lynch/HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis) in one lineage One affected individual should be a first-degree relative of the other two At least two successive generations should be affected At least one HNPCC-associated cancer should be diagnosed before age 50 – Women with synchronous or metachronous endometrial and colorectal cancer with the first cancer diagnosed before age 50

colon cancer, endometrial cancer, or other gastrointestinal or urinary tract cancers, and these patients sometimes develop ovarian cancer as well. This syndrome is caused by mutation of DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), and the lifetime risk of ovarian cancer is 9–12% [18, 19]. In patients with a family history of certain cancers, a genetic background should be suspected, and genetic counseling and testing should be performed (Table 1.4) [20]. Note that the details of hereditary ovarian cancer are described in the following section.

Regarding the etiology of sporadic ovarian cancer, which accounts for the majority of this disease, continuous ovulation, excessive gonadotropin stimulation, excessive hormone stimulation, and pelvic inflammation have all been proposed as causes [21].

There is a theory that trauma to the ovarian epithelium through repeated ovulation is a factor contributing to the development of ovarian tumors, and it is thought that DNA damage occurs in epithelial cells during the course of repeated ovulation and epithelial repair, possibly leading to carcinogenesis. Ovarian cancer is more frequent among unmarried, nulliparous, or infertile women, as well as women who have used ovulation inducers [22–24]. On the other hand, ovarian cancer is less frequent among women with a history of oral contraceptive use, pregnancy, or breastfeeding. In other words, ovarian cancer occurs less frequently among women in whom ovulation has been inhibited either artificially or naturally [25, 26]. Although a long lifetime ovulatory period may also be a risk factor, there is no stable relationship between the age of first menstruation, first birth, or menopause and the risk of ovarian cancer.

In addition, high levels of gonadotropins and steroid hormones are considered to have a role in ovarian carcinogenesis. It is thought that inclusion cysts formed within the ovaries due to ovulation may undergo genetic transformation due to stimulation by steroid hormones such as estrogen. Considering that ovarian tumors are less frequent around puberty and more frequent around menopause [27], involvement of endocrinological factors is further suggested. It is also suspected that high steroid hormone levels in the tumor microenvironment may possibly facilitate malignant transformation. A diet high in animal fat, increased cholesterol intake, and resulting obesity (high body mass index) are also considered to increase the risk of ovarian cancer [28]. This may possibly be related to increased levels of endogenous steroid hormones (androgens and estrogens) associated with high fat intake. The reduced risk of ovarian cancer due to the use of oral contraceptives may be related to inhibition of ovulation and a decrease of gonadotropins [25]. In contrast, hormone replacement therapy (HRT) after menopause may be a risk factor for ovarian cancer along with breast cancer, endometrial cancer, and liver cancer [29–32].

With respect to pelvic inflammation, it is thought that as with ovulation, DNA damage triggered during repair of the ovarian epithelium due to inflammation may lead to tumorigenesis. Exogenous substances such as talc and asbestos may also possibly increase the risk of ovarian cancer [33], while tubal ligation and hysterectomy are thought to be related to a lower risk of ovarian cancer because these procedures prevent carcinogenic substances from reaching the ovaries [34]. However, the incidence of ovarian cancer in patients undergoing these operations could be reduced by intraoperative examination of the ovaries and removal of asymptomatic early ovarian cancer, so the direct effect is unclear. Among internal factors, pelvic inflammatory disease (PID) is considered to increase the risk of ovarian cancer [35], and there is also a risk of precancerous change associated with endometriosis [36].

Conclusion

Both the incidence rate and mortality of ovarian cancer were increasing in the past but have stabilized or been decreasing in recent years. Regional differences seem to be decreasing in developed countries along with advances in and standardization of surgical treatment and chemotherapy, better understanding of risk factors, and widespread use of oral contraceptives. On the other hand, there are still regional differences based on racial/ethnic differences, and genetic background of this cancer has been attracting attention in recent years. As differences in the response to treatment may also be related to such differences, close attention must be paid to future epidemiological trends.

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