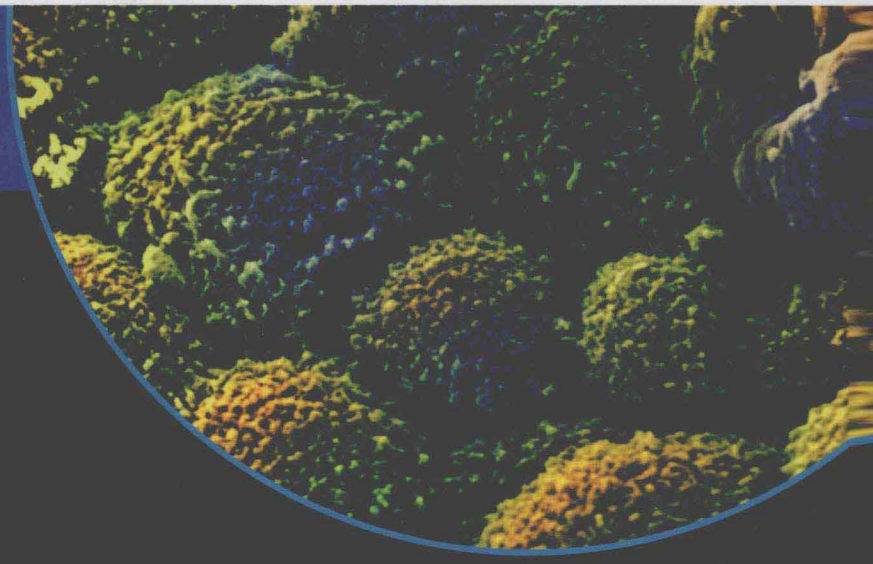

Early Diagnosis and Treatment of Cancer

OVARIAN

EDITED BY
Robert E. Bristow and Deborah K. Armstrong

SERIES EDITOR
Stephen C. Yang

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EARLY DIAGNOSIS AND TREATMENT OF CANCER

Series Editor: Stephen C. Yang, MD

Ovarian Cancer

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Series Preface

Seen on a graph, the survival rate for many cancers resembles a precipice. Discovered at an early stage, most cancers are quickly treatable, and the prognosis is excellent. In late stages, however, the typical treatment protocol becomes longer, more intense, and more harrowing for the patient, and the survival rate declines steeply. No wonder, then, that one of the most important means in fighting cancer is to prevent or screen for earlier stage tumors.

Within each oncologic specialty, there is a strong push to identify new, more useful tools for early diagnosis and treatment, with an emphasis on methods amenable to an office-based or clinical setting. These efforts have brought impressive results. Advances in imaging technology, as well as the development of sophisticated molecular and biochemical tools, have led to effective, minimally invasive approaches to cancer in its early stages.

This series, *Early Diagnosis and Treatment of Cancer*, gathers state-of-the-art research and recommendations into compact, easy-to-use volumes. For each particular type of cancer, the books cover the full range of diagnostic and treatment procedures, including pathologic, radiologic, chemotherapeutic, and surgical methods, focusing on questions like these:

- What do practitioners need to know about the epidemiology of the disease and its risk factors?
- How do patients and their families wade through and interpret the many tests they face?
- What is the safest, quickest, least invasive way to reach an accurate diagnosis?
- How can the stage of the disease be determined?
- What are the best initial treatments for early-stage disease, and how should the practitioner and the patient choose among them?
- What lifestyle factors might affect the outcome of treatment?

Each volume in the series is edited by an authority within the subfield, and the contributors have been chosen for their practical skills as well as their research credentials. Key Points at the beginning of each chapter help the reader grasp the main ideas at once. Frequent illustrations make the techniques vivid and easy to visualize. Boxes and tables summarize recommended strategies, protocols, indications and contraindications, important statistics, and other essential information. Overall, the attempt is to make expert advice as accessible as possible to a wide variety of health care professionals.

For the first time since the inception of the National Cancer Institute's annual status reports, the 2008 "Annual Report to the Nation on the Status of Cancer," published in the December 3 issue of the *Journal of the National Cancer Institute*, noted a statistically significant decline in "both incidence and death rates from all

cancers combined." This mark of progress encourages all of us to press forward with our efforts. I hope that the volumes in *Early Diagnosis and Treatment of Cancer* will make health care professionals and patients more familiar with the latest developments in the field, as well as more confident in applying them, so that early detection and swift, effective treatment become a reality for all our patients.

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Preface

Worldwide, 204,449 new cases of ovarian cancer are diagnosed each year, with an estimated 124,860 disease-related deaths.[1] In the United States, ovarian cancer is the leading cause of gynecologic cancer–related morbidity and mortality in large part due to the difficulty in detecting early-stage disease. One of the primary reasons that ovarian cancer is associated with such a significant burden of disease for the individual and for society is that it is a difficult disease to prevent, or at the very least diagnose in the early stages, when cure is still an attainable goal for the majority of patients. This volume discusses the full range of diagnostic and therapeutic considerations, including epidemiologic, pathologic, radiologic, surgical, and chemotherapeutic aspects. The volume is intended as a practical guide and overview to the diagnosis, staging, and management of patients with both early-stage and advanced-stage ovarian cancer.

Despite recent advances, the pathogenesis of ovarian cancer is still unclear, and one of the difficulties in studying ovarian cancer is the lack of a comprehensive tumor progression model. Ovarian cancer is a heterogeneous collection of tumors, which are primarily classified by cell type into serous, mucinous, endometrioid, clear cell, and Brenner (transitional) tumors corresponding to different types of epithelia in the organs of the female reproductive tract.[2–4] The tumors in each of the categories are further subdivided into three groups—benign, malignant, and intermediate (borderline tumor, or low-malignant-potential)—based on their clinical behavior. On the basis of a review of recent clinical, histopathologic, and molecular genetic findings, a research team has proposed a new carcinogenesis model that reconciles the relationship of borderline tumors to invasive carcinoma, discussed in Chapter 2.

The epidemiology of ovarian cancer has been extensively studied, and the most clinically relevant observations are presented in this volume. It is known that the incidence of ovarian cancer increases with age. Epithelial ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women, with 80% of ovarian cancers occurring after the age of 40. There are a number of demographic characteristics and factors related to reproductive history and health, including the so-called "incessant ovulation" theory and the associated effect of oral contraceptive use on reduction in risk, parity as a risk factor, and the interaction with infertility. Several environmental risk factors for ovarian cancer have also been targeted as potential contributors to pathogenesis. Perhaps the most significant known risk factor for ovarian cancer is a family history of the disease (or breast cancer) and the likelihood of a genetic predisposition. Approximately 10% of all ovarian cancers can be associated with a familial genetic predisposition. At present, the majority of hereditary ovarian cancers can be linked to two currently known syndromes, hereditary breast and ovarian cancer (HBOC) and hereditary nonpolyposis colorectal cancer (HNPCC).[5,6] HBOC syndrome is associated primarily with an increased risk for breast cancer, while HNPCC is associated with an increased risk for colorectal cancer. The most up-to-date information on ovarian cancer family syndromes is presented in Chapter 3. In addition, the indications and options for genetic testing of women at risk for ovarian cancer are also covered in detail.

At the current time, there have been no studies that demonstrate sufficient efficacy for ovarian cancer screening in the general population. Therefore, ovarian cancer screening is not recommended for women at general population risk. However, the urgency of ovarian cancer screening is greater for women with *BRCA1* and *BRCA2* mutations, given the significantly increased risk of ovarian cancer among these women. In Chapter 6, the basic principles of cancer screening, the challenges associated with ovarian cancer screening, and studies of screening strategies in high- and low-risk populations are reviewed. Because of the challenges of early detection of disease and the fact that genetic testing and screening will identify only a minority of patients who will ultimately develop ovarian cancer, chemical or surgical ovarian cancer prophylaxis may be considered for selected women. The various options for ovarian cancer prevention are reviewed in Chapter 4.

Radiographic imaging is an integral part of ovarian cancer detection, diagnosis, management, and treatment follow-up. A number of imaging modalities are available, and a variety of new techniques, especially molecular imaging approaches, are being developed. Each imaging modality has its unique advantages and limitations; therefore, evidence-based use of imaging is essential for achieving the greatest possible benefit without over- or underuse of specific modalities. New developments in radiographic imaging of ovarian cancer and the associated clinical applications are covered in Chapter 5.

Surgery is a cornerstone of the diagnosis and treatment of ovarian carcinoma. The surgical goals differ based on the nature and stage of disease. For patients with apparent early-stage disease, the primary surgical objective is to obtain sufficient pathologic documentation of the true extent of disease through a rigorous staging procedure. Accurate staging information allows low-risk patients to safely defer adjuvant chemotherapy and identifies patients at high risk of recurrence as those who will benefit from systemic treatment following surgery. Unfortunately, approximately 65% of patients will be diagnosed with International Federation of Gynecology and Obstetrics (FIGO) Stage III (T3N0/1M0) or IV (any T, any N, M1) disease.[7] For this group, the most important clinician-driven prognostic factors are the extent of residual disease following primary cytoreductive surgery and the administration of adjuvant platinum-based chemotherapy.[8,9] The most critical considerations for surgical intervention and selection of a chemotherapy treatment regimen for patients with both early-stage and advanced-stage ovarian cancer are reviewed in Chapters 7 and 8.

This volume is intended for all clinicians caring for women with ovarian cancer, including attending surgeons and physicians, fellows, and residents in the disciplines of gynecologic oncology, medical oncology, and primary care. Ultimately, the optimal management of ovarian cancer is dependent on multiple factors, including demographic prognostic factors, the age and general medical condition of the patient, the extent of disease at the time of detection, the biologic aggressiveness of disease, and available access to an appropriately skilled multidisciplinary care team. We hope that you enjoy this volume and benefit from the extensive experience of the elite team of contributors who have authored its contents.

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Contents

1 Epidemiology and Clinical Presentation of Ovarian Cancer

Namita Jhamb and Nicholas C. Lambrou

KEY POINTS

- Ovarian cancer is the leading cause of death from all gynecologic cancers in the United States.
- Median age of diagnosis is 63 years. Survival is related to race, age, and stage at diagnosis.
- Risk factors for ovarian cancer can be categorized as genetic, environmental, and reproductive.
- Nulliparity and infertility have been associated with an increased risk of ovarian cancer, whereas oral contraceptive use has a strong protective association.
- Family history is the most significant known risk factor. Hereditary breast-ovarian cancer syndrome and hereditary nonpolyposis colorectal cancer syndrome are the two clinically distinct syndromes associated with ovarian cancer.
- Environmental factors such as diet, obesity, and endometriosis have been associated with increased risk of ovarian cancer.
- The most common presenting symptoms include abdominal distention and bloating. Palpable pelvic mass is a common presenting sign.
- Serous papillary histology is the most common subtype of ovarian cancer, whereas mucinous and endometrioid histologies have been associated with improved prognosis in comparison.
- Optimal cytoreduction defined by residual disease less than 1 cm is associated with improved survival.
- CA-125 is well established for assessment of tumor response and detection of recurrent disease.

Introduction

Ovarian cancer is the leading cause of mortality from gynecologic cancers in the United States. In 2009, an estimated 21,550 women will be diagnosed with ovarian cancer and 14,600 will die of the disease.[1] It is the fifth most common cancer in women in the United States, and the fourth most common cause of death from malignancy[2] (Fig. 1-1). In the United States, an estimated 1 in 72 women will develop ovarian cancer in their lifetime (Table 1-1), and 1 in 100 will die from the disease.

Epidemiology

The incidence of ovarian cancer increases with age. Epithelial ovarian cancer is predominantly a disease of perimenopausal and postmenopausal women, with 80% of ovarian cancers occurring after age 40. Based on the cancer registry data collected by the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute, the median age at diagnosis for cancer of the ovary is 63 years. Age-specific incidence analysis reveals the following percentages of age at diagnosis of ovarian cancer:

1.2%—20 years
3.5%—20 to 34 years
8.1%—35 to 44 years
18.6%—45 to 54 years
21.4%—55 to 64 years
20.8%—65 to 74 years
19.4%—75 to 84 years
7.0%—≥85 years

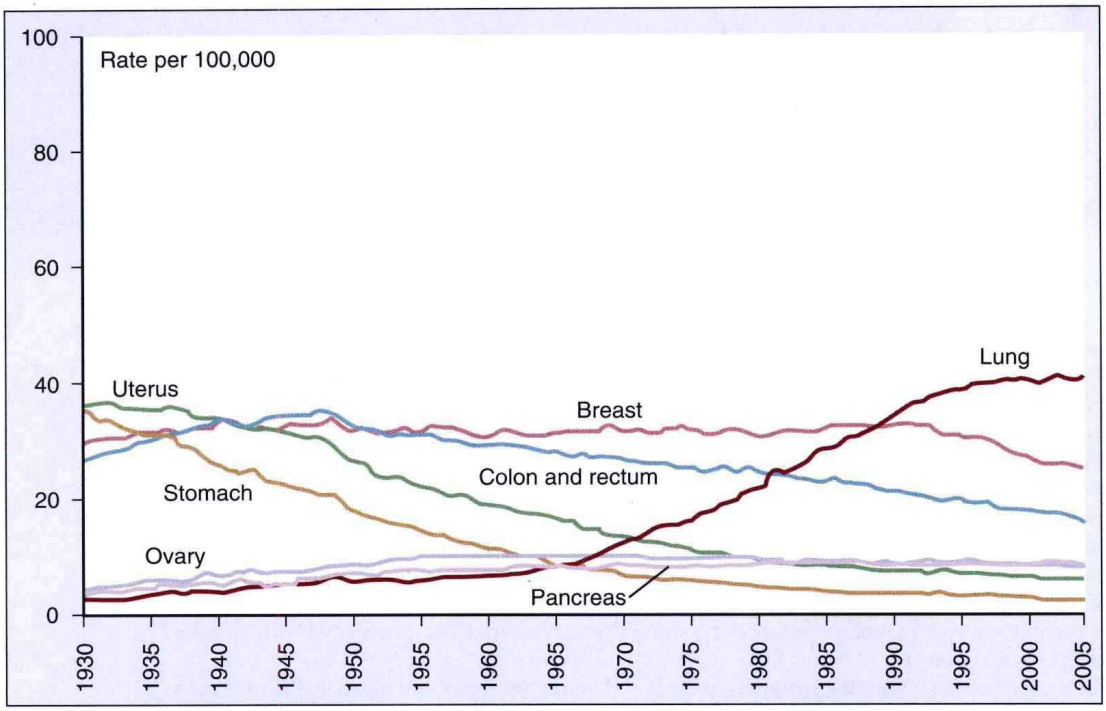

Figure 1-1. Cancer death rates for women, United States, 1930–2005 (per 100,000 women). Rates are age-adjusted to the 2000 U.S. standard population. (From US Mortality Public Use Data Tapes, 1960–2005, US Mortality Volumes, 1930–1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2008. American Cancer Society, *Cancer Facts & Figures 2009*. Atlanta: American Cancer Society, Inc., 2009.)

Table 1-1. Lifetime Probability of Developing Cancer by Site in Women, United States, 2002–2004*

Site	Risk
All sites†	1 in 3
Breast	1 in 8
Lung and bronchus	1 in 16
Colon and rectum	1 in 20
Uterine corpus	1 in 40
Non-Hodgkin lymphoma	1 in 53
Melanoma§	1 in 58
Ovary	1 in 72
Pancreas	1 in 75
Urinary bladder‡	1 in 84
Uterine cervix	1 in 145

**For those free of cancer at beginning of age interval.*
†All sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.
‡Includes invasive and in situ cancer cases.
§Statistic for white women.
From DevCan: Probability of Developing or Dying of Cancer Software, Version 6.2 Statistical Research and Applications Branch, NCI, 2007, http://srab.cancer.gov/devcan.

Table 1-2. Incidence Rates by Race

Race/Ethnicity	Incidence
All races	13.3 per 100,000 women
White	14.1 per 100,000 women
Black	10.1 per 100,000 women
Asian/Pacific Islander	9.8 per 100,000 women
American Indian/Alaska native	11.3 per 100,000 women
Hispanic	11.7 per 100,000 women

Data from Ries LAG, Harkins D, Krapcho M, et al: (eds): SEER Cancer Statistics Review, 1975–2005, National Cancer Institute. Bethesda, MD. http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site 2008. http://www.seer.cancer.gov/

Women with ovarian cancer and age younger than 50 have a 5-year survival rate of 70.5% compared with 40.6% in those 50 or older.[3] Survival is related to stage at diagnosis. In recent studies of the Gynecologic Oncology Group (GOG), the progression-free survival after platinum-paclitaxel chemotherapy following optimal cytoreduction was 21 to 22 months, and the median overall survival was 52 to 57 months.[4,5]

The average incidence of ovarian cancer in African-American women is 10.1 per 100,000 women compared with 14.5 per 100, 000 white women.[1] However African-American women have poorer survival rates compared with whites regardless of socioeconomic status.[6] A review of cases of epithelial ovarian cancer submitted to the National Cancer Database between 1985 and 1988 and between 1990 and 1993 revealed that African-American women were two times more likely than white women not to receive appropriate treatment. They had poorer survival rates than white women from the same or different hospitals, regardless of income. Among staged cases, African-American women were more often diagnosed with stage IV disease than were white women. The incidence rates by race are shown in Table 1-2. The majority of ovarian cancers are sporadic. The overall risk of developing ovarian cancer for women in the United States is 1.0% to 1.8%. For women with family history of ovarian cancer, the risk increases to 9.4%.[7]

Risk Factors

The epidemiology of ovarian cancer is multifactorial, with genetic, environmental, and reproductive factors directly or indirectly related to carcinogenesis.

Reproductive Factors

Incessant ovulation has been proposed as one of the primary causes of epithelial ovarian cancer. The ovarian epithelial cells proliferate after ovulation, which may propagate mutations or promote carcinogenesis.[8] Ovulation itself has been implicated in malignant transformation of the epithelium. Various epidemiologic studies have attempted to estimate women's total duration of ovulatory life based on reproductive and contraceptive histories. Purdie and associates[9] considered the effects of age-specific ovulation on ovarian cancer risk and found the highest risk for ovulations in the 20- to 29-year age group (odds ratio [OR] = 1.20 for each ovulatory year in this age group). For age groups 30 to 39 and 40 to 49 years, the odds ratios were 1.06

and 1.04, respectively. Therefore, suppression of ovulation in the 20- to 29-year age group would provide maximal reduction in risk of developing ovarian cancer.

Nulliparity is a known risk factor for ovarian cancer. Women who have ever been pregnant have a 30% to 60% reduction in ovarian cancer risk compared with nulliparous women.[10] Ovarian cancer risk is inversely related to parity (OR = 0.59 for four or more pregnancies compared with nulliparous women).[11] No significant association between ovarian cancer risk and young age at menarche has been seen in recent studies. However late menopause may be associated with a trend toward higher risk for ovarian cancer risk.[11,12]

There is a strong protective association between oral contraceptives and ovarian cancer. The decline in incidence and mortality rates in ovarian cancer among younger women in the United States has been associated with increased oral contraceptive use. The overall estimated protection from cohort and case-control studies is approximately 40% in women who have ever used oral contraceptives and increases with duration of use to more than 50% for users of 5 years or longer. The favorable effect of oral contraceptives against ovarian cancer risk persists for at least 10 to 15 years after use has ceased, and it is not confined to any particular type of oral contraceptive formulation.[13] The risks in ever-users is appreciably lower in women who reported their first oral contraceptive use before 25 years of age (relative risk [RR] = 0.3 for first use before age 25, 0.8 for first use at age 25 to 34, and 0.7 at 35 years or after).[14] The Cancer and Steroid Hormone Study suggested that 10 years of oral contraceptive use by women with a family history of ovarian cancer appeared to reduce their risk to levels lower than those of women with no family history of ovarian cancer who never used oral contraceptives. Similarly, 5 years of oral contraceptives by nulliparous women was projected to reduce their risk to the levels seen for parous women who never use oral contraceptives.[15] Lactation has been associated with a slight additional reduction in risk of ovarian cancer.[16] Women who breastfeed only 1 to 2 months have a relative risk of ovarian cancer of 0.6 compared with that of women who never breastfed, with this effect being most prominent with the first exposure.[17]

Infertility alone is an independent risk factor for ovarian cancer. The possible link between fertility drugs and ovarian cancer remains controversial. Various studies have focused on the risk of ovarian cancer after use of fertility agents. A meta-analysis of eight case-control studies showed that neither longer duration of fertility drug use nor unsuccessful fertility drug use was independently associated with significant elevations in adjusted cancer risk. Women who did not achieve a pregnancy after prolonged use of infertility drugs had a higher risk of developing borderline serous tumors, but not invasive tumors.[18] No association between fertility drugs, ovulation-inducing agents, and clomiphene citrate and ovarian cancer has been observed when comparing parous with nulliparous women.[19]

Few studies have examined the association of ovarian cancer after in vitro fertilization (IVF). During in vitro fertilization, multiple folliculogenesis is achieved by intensive ovulation induction. Both ovulation induction and ovarian puncture have been associated in the past with ovarian cancer.[20] However, more recent studies show no excessive risk of ovarian cancer in patients after completion of IVF when compared with the general population.[21,22]

Data from earlier epidemiologic studies did not show a clear association between hormone replacement therapy and ovarian cancer.[23] However, more recent studies suggest an association between long duration of use of unopposed estrogen and ovarian cancer.[24–26] The Women's Health Initiative Randomized Trial provided additional support regarding the effects of estrogen and progesterone on risks of ovarian cancer. The hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval [CI] =

0.77 to 3.24).[27] The National Institutes of Health–AARP Diet and Health Study Cohort included 97,638 women age 50 to 71 years. Use of unopposed estrogen for fewer than 10 years was not associated with ovarian cancer. Compared with no hormone therapy, use of unopposed estrogen for 10 or more years was statistically significantly associated with ovarian cancer among all women (RR = 1.89, 95% CI = 1.22 to 2.95; $P = .004$; 56 versus 72 ovarian cancers per 100,000 person-years, respectively) and, though not statistically significant, among women with hysterectomy (N = 19,359, RR = 1.70, 95% CI = 0.87 to 3.31; $P = .06$). Compared with women with intact uteri who never used hormone therapy, women who used estrogen and progestin had a statistically significant increased risk of ovarian cancer. (RR = 1.50, 95% CI = 1.03 to 2.19; $P = .04$). Risks of ovarian cancer were higher for women taking sequential (RR = 1.94, 95% CI = 1.17 to 3.22; $P = .01$) than continuous (RR = 1.41, 95% CI = .90 to 2.22; $P = .14$) regimens[28] (Table 1-3). Given the data, women who take hormone replacement therapy for more than 10 years should consider the potential increased risk for ovarian cancer when deciding to discontinue.

Genetic Factors

A family history of ovarian cancer is the most significant known risk factor. Approximately 10% of all ovarian cancers can be associated with a familial genetic predisposition. The risk depends on the number of first- and second-degree relatives with ovarian cancer and their age at diagnosis. A woman with a single family member affected by ovarian cancer has a 4% to 5% lifetime risk of developing the disease. This risk increases to about 7% if two family members are affected[3] (Table 1-4).

Approximately 7% of ovarian cancer patients have a positive family history of ovarian cancer, of whom 3% to 9% may eventually manifest certain hereditary cancer syndromes. Two clinically distinct syndromes are associated with hereditary ovarian cancer for which pedigree analysis suggests an autosomal dominant transmission with variable penetrance. Therefore, inheritance of these genetic mutations may occur from the maternal or paternal side. The hereditary breast-ovarian cancer syndrome (HBOC) is the more common of the two and is associated with germline mutations in *BRCA1* and *BRCA2* tumor suppressor genes. A lesser proportion is associated with the inherited form of endometrial and colorectal cancer known as hereditary nonpolyposis colorectal cancer (HNPCC).

The *BRCA1* gene is located on the long (q) arm of chromosome 17 at position 21 (17q21), and the *BRCA2* gene is localized to the long arm of chromosome 13 (13q12). Both *BRCA1* and *BRCA2* gene mutations are associated with a predisposition to breast and ovarian cancer. These mutations are mainly of the frameshift or nonsense variety. *BRCA1* is a tumor suppressor gene that acts as a negative regulator of tumor growth. Following the recognition of DNA damage, *BRCA1* is activated, which then may be involved in the transcription-coupled repair of oxidative DNA damage. Activated *BRCA1* is also likely to function as a transcription factor in regulation of complex genetic program that responds to DNA damage. Without a functional *BRCA1* or *BRCA2* gene, repair fails, leading to activation of p53-dependent DNA damage. A clinically significant mutation in *BRCA1* confers a lifetime risk of ovarian cancer of 40% to 50% compared with 20% to 30% risk associated with a *BRCA2* mutation.[29] In women with a *BRCA1* or *BRCA2* mutation, the risk of ovarian and breast cancer may be as high as 54% and 82%, respectively.[30] Most ovarian cancers associated with germline *BRCA* mutations are diagnosed at a younger age and are high-grade, advanced-stage serous carcinomas. Mutation rates for these genes have been reported to be as high as 8% to 10% in the general population.[31,32]

Women of Ashkenazi Jewish descent have been found to have an increased risk of inheriting *BRCA* mutations. About 40% of ovarian cancers in this population are

Table 1-3. Associations between Unopposed Estrogen Therapy–Only Use and Ovarian Cancer among Women Enrolled in the National Institutes of Health–AARP Diet and Health Study Cohort*

	All Women (*N* = 97,638)				Women with Hysterectomy (*N* = 19,359)			
Exposure	**No. of Cancers**	**Person-years**	**RR† (95% CI)**	***P* Value‡**	**No. of Cancers**	**Person-years**	**RR§ (95% CI)**	***P* Value‡**
No HT use	87	176,376	1.00 (referent)		14	25,030	1.00 (referent)	
Only ET	49	71,815	1.33 (0.89–2.00)	.17	37	51,455	1.23 (0.67–2.27)	.43
Recency of use								
Former	14	23,539	1.15 (0.65–2.05)		6	10,355	1.03 (0.40–2.70)	
Current	34	47,284	1.46 (0.89–2.38)	.13	31	40,638	1.37 (0.72–2.62)	.32
Duration of use (yr)								
<10	23	43,458	1.15 (0.72–1.82)		11	25,971	0.84 (0.38–1.88)	
≥10	26	27,501	1.89 (1.22–2.95)	.004	26	24,990	1.70 (0.87–3.31)	.06
Recency and duration								
Former	14	23,539	1.16 (0.65–2.07)		6	10,355	1.07 (0.41–2.78)	
Current (yr)								
<10	10	22,497	1.00 (0.49–2.03)		7	17,481	0.83 (0.33–2.09)	
≥10	24	24,603	1.88 (1.08–3.27)	.06	24	22,994	1.71 (0.87–3.35)	.14

CI, confidence interval; ET, unopposed estrogen therapy; HT, hormone therapy; RR, relative risk.

**Among all women, recency of use was unknown for one woman who developed ovarian cancer and 992 person-years, duration of use was unknown for 857 person-years, and recency and duration were unknown for 1177 person-years. Among women with hysterectomy, recency of use was unknown for 462 person-years, duration of use was unknown for 494 person-years, and recency and duration were unknown for 625 person-years.*

†Relative risks adjusted for continuous age (years), race (white, other/unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), body mass index (BMI) (<25, 25–29, ≥30 kg/m^2 or unknown), and menopause and hysterectomy (natural menopause, surgical menopause, premenopause, or unknown); models include terms for ever use of other HT formulations (ET followed by estrogen plus progestin, estrogen plus progestin only, progestin followed by estrogen plus progestin, ET and estrogen plus progestin but order unknown, other formulations, or unknown).

‡P values (two-sided) were calculated using Wald chi–square tests of categorical (ever-use) or ordinal (recency of use and recency and duration) variables based on the categories and referent group shown. The P value (two-sided) for duration of use was based on an ordinal variable for total years of use at baseline (none, 1, 2, 3, . . . , 9, 10, or >10).

§Relative risks adjusted for continuous age (years), race (white, other/unknown), duration of oral contraceptive use (none, <10 years, ≥10 years, or unknown), and BMI (<25, 25–29, ≥30 kg/m^2 or unknown).

From Lacey JV, Brinton LA, Leitzmann MF, et al: Menopausal hormone therapy and ovarian cancer risk in the National Institutes of Health-AARP Diet and Health Study Cohort. NCI J Natl Cancer Inst 98:1397–1405, 2006.