

Samir A. Farghaly
Editor

Advances in Diagnosis and Management of Ovarian Cancer

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Samir A. Farghaly, MD, PhD
Department of Obstetrics
and Gynecology
Weill Cornell Medical College
The New York Presbyterian
Hospital-Weill Cornell Medical Center
Cornell University
New York, NY
USA

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This book is dedicated to the memory of my mother, Amina, and my father, Aly, who had a great influence on me and my academic and professional medical career. To my late siblings, Nabil and Magdy, and their families. Also, to my sisters, Sorya and Nadia, my brother, Raafat and their families. In addition, to my beloved children, Raied and Tamer.

Moreover, I dedicate this book to the memory of Hugh R.K. Barber, M.D., who passed away in 2006. He was a leader in the field of Gynecologic Oncology and was internationally renowned for his seminal work in ovarian cancer. He was Chairman of the Department of Obstetrics and Gynecology at Lenox Hill Hospital Medical Center, New York, NY, USA. I had the pleasure of meeting him in 2005, and having several extensive discussions about the topic of ovarian cancer, he was an inspiration to me and my current book.

Samir A. Farghaly, MD, PhD

Foreword

The importance of this book is included in its very theme, as it presents gynecological cancer of the most unfavorable prognosis. In fact, despite the numerous advances in surgery, chemotherapy, and molecular therapies, the survival rates have only slightly improved. Selecting ovarian tumors as the object of study, as assessed by a multi-specialized team, can assist the gynecological oncologists, and also refine the approach to the disease and increase their professional standard.

This book, written by 32 international acknowledged experts, with rich and clear illustrations, offers an expert guide to all aspects of this neoplasia.

From the epidemiology, through risk, management in early and advanced stages, pediatric neoplasia, to the quality of life, the author explores all the possible aspects of this disease and all the implications that affect the outcome.

The chapters are all written very clearly, allowing anyone from the student to the expert to fully benefit from consultation of the manual, and the in-depth information makes it easier to understand its contents.

In conclusion, I believe that the comprehensive text conveys a significant progress in understanding this complex neoplasia.

Montreal, Canada

Dr. (Med) Maria Marchetti

Preface

Worldwide, 204,449 new cases of ovarian cancer are diagnosed each year, with an estimated 124,860 disease-related deaths. There are notable differences in ovarian cancer incidence across the world. In Europe, in 2012, there were 65,538 cases with a mortality rate of 42,704 women. The American Cancer Society's estimates for ovarian cancer in the USA for 2013 are: about 22,240 women will receive a new diagnosis of ovarian cancer and about 14,230 women will die from the disease. The ovarian cancer statistics for incidence indicates it is highest in the USA and Northern Europe and lowest in Africa and Asia. Ovarian cancer is the ninth most common cancer among women, excluding nonmelanoma skin cancers. It ranks fifth in cancer deaths among women. It accounts for about 3 % of all cancers in women. A woman's risk of getting ovarian cancer during her lifetime is about 1 in 72. Her lifetime chance of dying from ovarian cancer is about 1 in 100. Incidence rates of ovarian cancer increase with age, becoming more prevalent in the eighth decade of life. Patients are typically diagnosed when the disease has metastasized (stage III or IV) which has an overall survival rate between 5 and 25 %.

Five-year survival in ovarian cancer has doubled over the past 30 years, increasing from approximately 25 % to 50 %. This is a result of developments in diagnosis and more efficient management. Clearly, there is more room to increase this rate to a higher number. This could be achieved by developing novel tests for early detection and diagnosis and innovative medical therapy and surgical techniques. The ideal approach to women with ovarian cancer is a multidisciplinary one, with many professionals contributing to the excellent care and outcome that we wish to see for those individuals we are privileged to look after.

This book discusses a range of early diagnostic and therapeutic considerations, including epidemiologic, molecular genetic testing, histopathologic, open surgical, minimally invasive surgical, and targeted molecular therapy for patients with hereditary and nonhereditary ovarian cancer.

The importance of updated knowledge of the epidemiology of ovarian cancer as it affects primary prevention, early detection, and possibly therapeutic strategies is discussed in Chap. 1. The risk of developing breast/ovarian cancer in women with BRAC1 and BRAC2 mutant genes and the molecular genetic testing of these genes and others are discussed in Chap. 2. The risk management of hereditary ovarian cancer such as surveillance,

chemoprevention, and prophylactic surgery is detailed in Chap. 3. The development and evaluation of improved biomarker-based tests and recent advances in this arena are discussed in Chap. 4.

The origin, histopathologic, and molecular genetic aspects of surface epithelial tumors of the ovary are detailed in Chap. 5. The immunohistochemical and molecular pathological aspects of non-epithelial ovarian cancer, as it presents unique clinical diagnostic and therapeutic challenges, are outlined in Chap. 6. The management strategies in early-stage, late-stage, and recurrent ovarian cancer are detailed in Chap. 7. The recent advances in diagnosis and management of ovarian neoplasms in the pediatric female population of less than 17 years old are discussed in Chap. 8. Comprehensive current management of patients with early-stage ovarian cancer, including the role of minimally invasive surgery and fertility sparing surgery for young women, is detailed in Chap. 9. The importance of aggressive surgical debunking and novel chemotherapy regimens, including intraperitoneal chemotherapy in patients with late-stage ovarian cancer is outlined in Chap. 10. The intraperitoneal chemotherapy administration and its complication in patients with peritoneal carcinomatosis secondary to epithelial ovarian cancer are detailed in Chap. 11. As a novel therapeutic option, targeted molecular genetic therapy for patients with ovarian cancer is detailed in Chap. 12. Variety of quantities and qualitative assessment of the psychological impact of ovarian cancer and the positive impact of cancer experience are outlined in Chap. 13. Finally, the importance of quality of life (QOL) as an outcome on both disease and treatment decision making in patients affected with ovarian cancer is detailed in Chap. 14.

This book 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, surgical oncology, medical oncology, and primary care. Allied medical staff, palliative services, and nurse specialists will also find it a useful adjunct to getting current information on diagnosis and management of ovarian cancer.

I hope that you enjoy this book and benefit from the extensive experience of the internationally renowned contributors to this book from the USA, UK, and Italy who have authored its contents.

New York, NY, USA

Samir A. Farghaly, MD, PhD

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Contributors

Kate Absolom, PhD, BSc (Hons) Psychosocial Oncology and Clinical Practice Research Group, Leeds Institute of Molecular Medicine, Division of Cancer Studies and Pathology, University of Leeds, Leeds, UK

Caterina Accettura, MD Department of Oncology, Vito Fazzi Hospital, Lecce, Italy

Andrea Besharat, MPH Division of Population Sciences, Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

John Butler, MD Department of Gynaecological Oncology, St Bartholomew's Hospital, West Smithfield, London, UK

David Cella, PhD Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Samir A. Farghaly, MD, PhD Department of Obstetrics and Gynecology, The Weill Cornell Medical College/Weill Cornell Graduate School of Medical Sciences, and The New York Presbyterian Hospital-Weill Cornell Medical Center, Cornell University, New York, NY, USA

Anne C. Fischer, MD, PhD Department of Pediatric Surgery, William Beaumont Hospital, Royal Oak, MI, USA

Department of Surgery, Oakland University William Beaumont Medical School, Royal Oak, MI, USA

Christopher A. Friedrich, MD, PhD Division of Oncology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA

Marianna Giampaglia, MD Department of Oncology, Vito Fazzi Hospital, Lecce, Italy

Marilena Greco, PhD, BSc Laboratory of Medical Genetics, Giovanni Paolo II Oncological Centre, Lecce Hospital, Lecce, Italy

Sarah Gustapane, MD Department of Obstetrics and Gynecology, SS. Annunziata Hospital, Chieti, Italy

Geoff Hall, MB, ChB, MRCP, PhD, FRCP Department of Oncology, University of Leeds/St James's Institute of Oncology, Leeds, UK

Cyril W. Helm, MB.BChir Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead, Tyne and Wear, UK

Eleni Ieremia, FRCPath Department of Cellular Pathology, Barts Health NHS Trust, London, UK

Sally E. Jensen, PhD Department of Medical Social Sciences and Department of Surgery, Division of Organ Transplantation, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

Alexandra Lawrence, MD, MRCOG Department of Gynaecological Oncology, St. Bartholomew's Hospital, West Smithfield, London, UK
Queen's Hospital, Rom Valley Way, Romford, UK

Silvana Leo, MD Department of Oncology, Vito Fazzi Hospital, Lecce, Italy

Anna E. Lokshin, PhD University of Pittsburgh Cancer Institute, Hillman Cancer Center, Pittsburgh, PA, USA
Departments of Medicine, Pathology, and Ob/Gyn, School of Medicine, University of Pittsburgh, Pittsburgh, PA, USA

Vito Lorusso, MD Department of Medical Oncology, National Institute for Cancer Research, Istituto Tumori Giovanni Paolo II, Bari, Italy

Michele Maffia, PhD Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy

Purnima Makhija, MD Department of Cellular Pathology, Barts Health NHS Trust, London, England, UK

Antonio Malvasi, MD Department of Obstetrics and Gynecology, Santa Maria Hospital, Bari, Italy

Tim Mould, MD, FRCOG, MBBS, MA, DM, FRCOG Department of Gynaecological Oncology, University College London, London, UK

Brian M. Nolen, PhD University of Pittsburgh Cancer Institute, Hillman Cancer Center, Pittsburgh, PA, USA

Jennifer Permuth-Wey, PhD Division of Population Sciences, Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Thomas A. Sellers, PhD Division of Population Sciences, Department of Cancer Epidemiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Naveena Singh, MBBS, FRCPath Department of Cellular Pathology, Barts Health NHS Trust, London, England, UK

Paul H. Sugarbaker, MD, FACS, FRCS Department of Center for Gastrointestinal Malignancies, Washington Cancer Institute, MedStar Washington Hospital Center, Washington, DC, USA

Elena Takeuchi, MB ChB, MRCP Psychosocial Oncology and Clinical Practice Research Group, St. James's Institute of Oncology, Leeds, UK

Andrea Tinelli, MD Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

Galina Velikova, BMBS(MD), PhD, FRCP Department of Oncology, University of Leeds/St James's Institute of Oncology, Leeds, UK

Daniele Vergara, BSc, PhD Department of Biological and Environmental Sciences and Technologies, University of Salento, Lecce, Italy

Epidemiology of Ovarian Cancer: An Update

1

Jennifer Permuth-Wey, Andrea Besharat,
and Thomas A. Sellers

Introduction

Ovarian cancer (OC) is the eighth most commonly diagnosed cancer among women in the world, accounting for nearly 4 % of all female cancers [1]. OC also represents the third leading gynecologic cancer, following cancer of the cervix and uterine corpus, and causes more deaths per year than any other cancer of the female reproductive system [1, 2]. On a worldwide basis, an estimated 225,000 new cases are diagnosed and 140,000 women die of OC annually [1]. In 2011, approximately 22,000 new cases of OC were diagnosed and 15,500 OC-related deaths occurred in the United States [3]. A woman's risk of developing OC in her lifetime is 1 in 71, and her chance of dying of the disease is 1 in 95 [3]. Mortality is high because women typically present with late stage disease when the overall 5-year relative survival rate is 44 % [4]. Thus, the public health burden is significant.

Despite the high incidence and mortality rates, the etiology of this lethal disease is not completely understood. Research to identify the causes of

OC is sorely needed; such knowledge could inform strategies for risk assessment, prevention, surveillance, early detection, and treatment. The purpose of this chapter is to review some of the established and suspected epidemiologic risk factors for OC. We divide this chapter into four sections: the pathologic classification of OC, descriptive epidemiology, risk factors and protective factors, and summary and conclusions.

Pathologic Classification of Ovarian Cancer

Nearly all benign and malignant ovarian tumors originate from one of three cell types: epithelial cells, stromal cells, and germ cells. In developed countries, more than 90 % of malignant ovarian tumors are epithelial in origin, 5–6 % of tumors constitute sex cord-stromal tumors, and 2–3 % are germ cell tumors [2]. The pathology and classification of ovarian tumors are described in detail by Chen et al. [5]. Epidemiologic studies have suggested etiologic differences in these three cell types [6]. Most epidemiologic research, including the present review, focuses on epithelial OC because they are the predominant subtype. Malignant epithelial OCs, also known as carcinomas, are comprised of four main histologic subtypes: serous, clear cell, endometrioid, and mucinous [7]. Based on two population-based studies [8, 9], the relative frequencies of these four subtypes are 68–71, 12–13, 9–11, and 3 %, respectively. Within each of these categories

J. Permuth-Wey, PhD • A. Besharat, MPH
T.A. Sellers, PhD (✉)
Division of Population Sciences,
Department of Cancer Epidemiology,
H. Lee Moffitt Cancer Center and Research Institute,
12902 Magnolia Drive, MRC CAN-CONT,
Tampa, FL 33612, USA
e-mail: jenny.vey@moffitt.org;
andrea.besharat@rmpdc.org;
thomas.sellers@moffitt.org

are tumors of uncertain malignant behavior (known as “borderline tumors” or “tumors of low malignant potential”) that contain microscopic features of malignancy without frank invasion into surrounding stroma. Such borderline tumors are usually not included in the published statistics of most cancer-reporting systems [6]. However, the risk factors for OC seem to apply similarly for borderline and invasive epithelial tumors, although mean age at diagnosis is earlier among women with borderline tumors [10, 11].

It is important to point out that epithelial OCs themselves reflect a heterogeneous group of diseases. As reviewed by McCluggage [7], histologic subtypes differ in their cellular origin, the molecular alterations that mark their initiation and progression, and their natural behavior and prognosis. Furthermore, epidemiologic studies

suggest that the major histotypes of epithelial OC also have different risk factor profiles [10–17]. We will comment on some of these study findings throughout this chapter. Thus, it seems prudent to consider the histologic distribution of cases when designing, conducting, and interpreting OC research.

Descriptive Epidemiology

OC incidence exhibits wide geographic variation, as shown in Fig. 1.1 [1]. The highest age-adjusted incidence rates are observed in developed parts of the world, including North America and Western and Northern Europe, with rates in most of these areas exceeding 8 per 100,000. Rates are intermediate in South America (6.2 per 100,000)

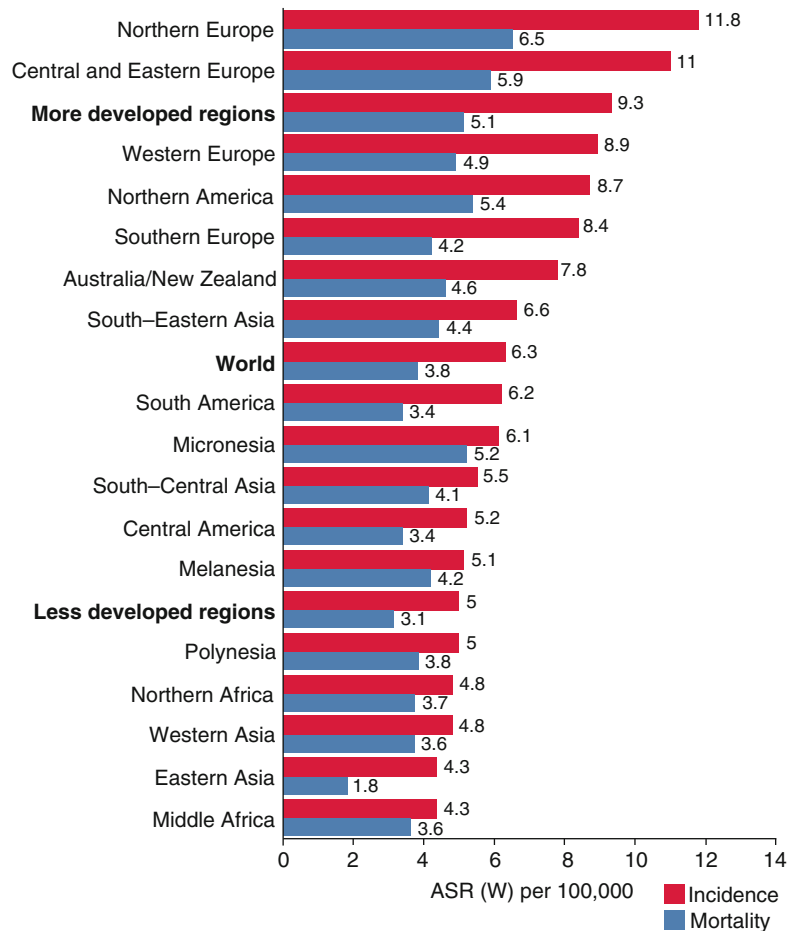


Fig. 1.1 Worldwide ovarian cancer incidence and mortality rates. Rates are per 100,000 and represent age-standardized rates according to the world standard population (ASR (W)) (From the International Agency for Research on Cancer [1])

Table 1.1 Age-adjusted ovarian cancer incidence and mortality rates in the United States by race

Race/ethnicity	Incidence rates ^a by race per 100,000 women	Death rates ^a by race per 100,000 women
All races	12.8	8.6
White	13.5	8.9
Black	10.0	7.2
Asian/Pacific Islander	9.9	4.9
American Indian/ Alaska Native	10.6	6.8
Hispanic	10.6	6.0

^aAge-standardized rates (world) per 100,000 women are based on cases diagnosed in 2004–2008 from 17 SEER Registries [4]

and lowest in Asia and Africa. Migration from countries with low rates to those with high rates results in greater risk [18, 19], underscoring the importance of nongenetic factors. However, even within the United States, racial differences in incidence and mortality are apparent that mimic the observed international variation (Table 1.1). Rates are highest among Whites, intermediate for Hispanics, and lowest among Blacks and Asians [4]. In most parts of North America and Europe, the incidence of OC was constant in the decades prior to the 1990s and has gradually declined since that time [4, 20–22]. The incidence of OC increases with age, with a median age at diagnosis of 63 years [4]. Approximately 88 % of OCs occur after age 45. In the United States, there has also been a gradual decline in OC-related mortality for all races combined [22].

Risk Factors and Preventive Factors

Inherited Susceptibility

One of the most significant risk factors for OC is a family history of the disease, which occurs among approximately 7 % of women with OC [23]. First-degree relatives of OC probands have a three- to sevenfold increased risk, especially if multiple relatives are affected and at early age at onset [24–28].

It is clear that a subset of OCs occurs as part of a hereditary cancer syndrome that is inherited in

an autosomal dominant pattern. The majority of hereditary OCs can be attributed to mutations in the *BRCA1* and *BRCA2* genes [29]. According to data from the Breast Cancer Linkage Consortium, the risk of OC through age 70 years is up to 44 % in *BRCA1* families [30] and approaches 27 % in *BRCA2* families [31]. Mutation screening of population-based series of OC cases has shown that 10–15 % of epithelial OCs can be attributed to mutations in either *BRCA1* or *BRCA2* [32–40]. In addition, OC occurs in families with hereditary nonpolyposis colorectal cancer syndrome (HNPCC), also known as Lynch syndrome [41]. The genetic defects underlying HNPCC (the mismatch repair genes *hMLH1*, *hMSH2*, *hPMS1*, *hPMS2*, and *hMSH6*) may account for at least 2 % of epithelial OC and confer up to a 20 % lifetime risk [4, 29, 42–45]. Overall, mutations in highly penetrant genes account for 10–15 % of epithelial OCs [46, 47]. Candidate gene studies such as those reviewed by Fasching et al. [48]. and genome-wide association studies [49–51] involving non-familial OC cases have identified more common, low-penetrant variants that may be associated with OC risk will be covered in Chap. 2.

Hormonal Risk Factors

Hormones such as estrogen and progesterone are believed to be involved in promoting ovarian carcinogenesis. An extensive review of the hormonal etiology of epithelial OC [52] concluded that there are two, not necessarily mutually exclusive, hypotheses that reflect what is currently known about the disease. The “incessant ovulation” hypothesis proposes that the number of ovulatory cycles increases the rate of cellular division associated with the repair of the surface epithelium after each ovulation, thereby increasing the likelihood of spontaneous mutations that may promote carcinogenesis [53]. Indeed, positive correlations exist between increasing numbers of lifetime ovulations and OC risk [54–57]. The second hypothesis, often referred to as the “gonadotropin hypothesis,” posits that gonadotropins such as luteinizing hormone and follicle-stimulating hormone overstimulate the

ovarian epithelium, causing increased proliferation and subsequent malignant transformation [58]. The epidemiology of OC does not help clearly distinguish between these two hypotheses.

The following sections review the epidemiologic data on both endogenous correlates of reproductive hormone exposure and exogenous sources of hormones, specifically oral contraceptives and hormone replacement therapy (HRT). For a more detailed summary of the hormonal aspects of OC, the reader is referred to a review by Riman et al. [59].

Age at Menarche and Age at Menopause

According to the incessant ovulation hypothesis, early age at menarche and late age at menopause could increase the risk for OC through an increased number of ovulatory cycles. Conversely, according to the gonadotropin hypothesis, a late age at menopause delays the surge of postmenopausal gonadotropin hormones, possibly reducing OC risk. Numerous epidemiologic studies have examined the relation between lifetime menstrual history and OC risk. Results of studies that have examined the age at onset of menses are not terribly consistent [60–70]. For example, in a collaborative analysis of 12 US case-control studies conducted between 1956 and 1986, data from 2,197 White OC cases and 8,893 White controls detected no elevation in risk among women with onset of menses before 12 years of age [66]. Similarly, no statistically significant association was detected in the prospective Nurses' Health Study cohort of 121,700 female registered nurses aged 30–55 years when the study began [69]. One Chinese study identified a significant protection with late age at menarche (after age 18) [71], while another study observed a slight increased risk with late age at menarche [72]. Additional research has failed to clarify the literature [53, 61, 73–78]. Data on age at natural menopause and OC risk are also inconsistent. Numerous case-control studies have identified an association between late age at menopause and the risk of OC, with odds ratios ranging from 1.4 to 4.6 in the highest category of age at menopause [60, 61, 63, 67, 71, 72, 76].

In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, age at menopause (>52 vs ≤ 45 years) was associated with an increased OC risk (HR = 1.57, 95 % CI: 1.16–2.13); however, after women diagnosed with OC within the first 2 years of follow-up were excluded, the risk was slightly attenuated and marginally statistically significant (HR = 1.40, 95 % CI: 0.98–2.00) [77]. The authors speculated that older women in the subclinical stage of OC may mistake bleeding for menses, which is why risk was attenuated when recently diagnosed cases were removed from the analysis. Other case-control studies [66, 68, 74, 75, 79–81] and several cohort studies [69, 73] found no such association. The collaborative analysis by Whittemore et al., for example, calculated an OR of 1.1 (95 % CI: 0.71–1.3) for menopause occurring after the age of 55 [66].

A recent study report from the Nurses' Health Study and Nurses' Health Study II found that age at natural menopause was associated with an increased risk of endometrioid tumors (RR = 1.13, 95 % CI: 1.04–1.22), but not serous invasive or mucinous tumors [17]. There are various explanations for the conflicting results regarding the relationship between ages at menarche and menopause and OC risk [82]. Besides the role of chance, it has been proposed that these differences may be explained through real differences between populations. Additionally, it is possible that the definition of menarche and menopause can be subject to recall and misclassification bias. It has also been pointed out that various populations have different age distributions and that some studies may have failed to adjust for age or other covariates in the analysis. In summary, it can be inferred from the available evidence that if early age at menarche and late age at menopause increase the risk of OC, the magnitude is likely small.

Pregnancy, Parity, and Infertility

The association between pregnancy and OC risk has been studied extensively. Pregnancy causes anovulation and suppresses secretion of pituitary gonadotropins. Both the "incessant ovulation" and the "gonadotropin" hypotheses would predict that pregnancy reduces the risk of OC. Indeed,

one of the most consistent findings is that parous women have a 30–60 % lower risk for OC than nulliparous women [53, 60, 67, 71–75, 80, 82–86]. Furthermore, each additional full-term pregnancy is estimated to lower risk by approximately 15 % [66, 73, 87]. While many case-control studies with hospital controls have shown positive associations with late age at first birth (≥ 30 years of age) [60, 65, 66, 74, 76, 83, 88–91], a reduced risk with late age at first birth has been identified in some case-control studies with population controls [64, 66, 92]. Recent data also suggests that OC risk does not vary by the time interval between the first and last birth [93].

It is unclear whether spontaneous or induced abortions impact OC risk. Although many investigations have found that an increased number of incomplete pregnancies may slightly decrease risk [53, 60, 65, 66, 72, 73, 94–96], others have reported risk to be increased among women with one or more incomplete pregnancies [75, 86], and a sizeable number of studies have yielded null results [64, 67, 68, 70, 74, 80, 83, 85, 97]. Induced abortions have been associated with lower risk in several studies [73, 95, 96], but not others [64, 76, 94]. With regard to spontaneous abortions and OC risk, positive [68, 83, 94], inverse [70], and null associations [71, 85, 95] have been reported. Interpretation of this literature is difficult because of the recognized potential for recall bias of spontaneous or induced pregnancies [59].

It is yet to be determined whether nulliparity and low parity per se, rather than difficulty becoming pregnant due to female infertility, is the relevant factor. Infertility is a term that is used to describe a heterogeneous group of biologically distinct conditions ranging from genital tract infections and tubal disturbances to medical conditions such as endometriosis and polycystic ovarian syndrome [98, 99]. Infertility appears to be associated with increased OC risk in most studies [60, 66, 70, 74, 80, 83, 85, 86, 91, 98], but not all [73, 100]. Infertility seems to pose the greatest risk among women who remain nulliparous, while periods of temporary infertility among parous women are of little concern [60, 66, 70, 74, 85]. For example, in a large Canadian case-control study in which most nul-

liparous women were so by choice, infertility was not associated with OC risk among parous women, but there was a trend towards elevated risk among a small group of infertile nulliparous women (OR=2.5, 95 % CI: 0.6–4.1) [70].

Possible reasons for the inconsistent results may include the failure to examine the various types of infertility separately. Furthermore, it has been reported that some factors such as a personal history of endometriosis [101–103] or polycystic ovarian syndrome [104] may influence both infertility and OC risk. The definition of infertility used across studies is variable, including physician-diagnosed infertility, self-reported infertility, and periods of unprotected intercourse without becoming pregnant [59]. A particular challenge is trying to distinguish an influence of infertility from an adverse effect of fertility drug exposure. Although some studies report that women with a prior history of fertility drug use who remain nulliparous are at an elevated risk for ovarian tumors, particularly tumors of low malignant potential [66, 105], the results are not consistent [98–100, 106–108]. Early detection bias may explain the discrepant findings, as early stage cancers may be overdiagnosed in infertile women due to the close medical surveillance [109].

Lactation

Lactation suppresses secretion of pituitary gonadotropins and leads to anovulation, particularly in the initial months after delivery [6]. If the incessant ovulation and gonadotropin hypotheses are true, lactation should reduce the risk of OC. Although the majority of studies have identified a slight decrease in OC risk with lactation, with odds ratios approximating 0.6–0.7 [66, 67, 70, 84–86, 110–113], some have not [64, 68, 80]. Despite the conflicting results, the overall impression is that lactation protects against epithelial OC, especially in the first few months following delivery.

Benign Gynecologic Conditions and Gynecologic Surgery

Several gynecologic conditions have been examined as risk factors for OC, including polycystic ovarian syndrome (PCOS), endometriosis, and

pelvic inflammatory disease (PID). PCOS is a heterogeneous disease often characterized by obesity, hirsutism, infertility, and menstrual abnormalities. The association between PCOS and OC risk was investigated using data from the Cancer and Steroid Hormone Study, a population-based case-control study [104]. Among 476 histologically confirmed epithelial OC cases and 4,081 controls, 7 cases (1.5 %) and 24 controls (0.06 %) reported a history of PCOS (OR=2.5-fold, 95 % CI: 1.1–5.9) [104]. The association appeared to be stronger among women who never used oral contraceptives (OR=10.5, 95 % CI: 2.5–44.2) and women in the first quartile of body mass index (13.3–18.5 kg/m²) at age 18 (OR=15.6, 95 % CI: 3.4–71.0), but these estimates have wide confidence intervals. Larger studies that adjust for potential confounders of the PCOS-OC association are needed before conclusions can be drawn regarding these findings.

Endometriosis is one of the most common gynecologic disorders, affecting 10–15 % of women in reproductive years [114]. Even though endometriosis is considered a benign condition, it has been linked with OC in the medical literature since 1925. Sayasneh and colleagues [114] recently reported a systematic review of eight studies; seven found an increased risk of OC, with effect sizes ranging from 1.3 to 1.9. The strongest associations were evident among endometrioid and clear cell histologies, consistent with molecular data that supports the uterus as the origin of these subtypes [7]. However, the authors suggest that the association between endometriosis and endometrioid and clear cell ovarian carcinomas may represent sharing of similar risk factors rather than a causal association [114], a topic that merits further research.

PID causes inflammation of the endometrium, fallopian tubes, and ovaries. Previous studies from the 1990s that evaluated the association between PID and OC risk yielded inconsistent results [115, 116]. Recently, Lin and colleagues [117] evaluated this association in a large nationwide cohort from Taiwan that included 67,936 women with PID (42 of whom later developed OC) and 135,872 women without a history of PID (48 of whom developed OC). A history of

PID was found to be a risk factor (adjusted HR=1.92 (95 % CI: 1.27–2.92)), especially among subjects diagnosed with PID before the age of 35 and women who had at least five episodes of PID. Note, however, that the absolute rates of OC among women with PID are clearly low overall.

Several gynecologic procedures appear to influence the risk for OC. It is well established that among high risk women, bilateral prophylactic oophorectomy decreases OC risk by at least 90 % [118]. Numerous studies have identified a reduced risk of OC associated with either a hysterectomy or tubal ligation (without oophorectomy), with the protective effect for each of these procedures ranging from 30 to 40 % [60, 70, 119–124]. For example, a recent meta-analysis estimated that tubal ligation reduced OC risk by 34 % [125]. Furthermore, the risk reduction from these procedures appears to last for at least 10–15 years, which argues against screening bias (due to selective removal of subclinical ovarian tumors) as the basis for the findings [81, 120, 126, 127]. Although it is uncertain how these procedures reduce the risk of OC, removal of the uterus and/or blockage of the tubes may prevent potential carcinogens from ascending the genital tract [62] and decreases blood flow to the ovaries [127]. In particular, Vercillini and colleagues [128] hypothesize that retrograde menstruation (i.e., menstrual fluid flows backwards into the fallopian tubes instead of leaving the body through the vagina) may promote iron-induced oxidative stress and subsequent cancer development in the fallopian tubes and ovaries.

Oral Contraceptives (OC) and Other Forms of Contraception

The 30–40 % lower risk of ovarian cancer among women who ever used oral contraceptives is firmly established. The findings are consistent over the past several decades, even as the drug formulations evolved from high estrogen and progestin content popular in the 1960s to decreasing hormone content in the mid-1970s, and in the early 1980s when the sequential compounds (biphasic and triphasic) were introduced [129]. The risk reduction increases with duration of use

[66, 70, 130–133] by at least 5 % per year, with about a 50 % reduction in risk for long-term use of 10 years or greater, [134] and persists long after use has ceased [80, 84, 132, 135–138]. Moreover, the risk reduction is not confined to any particular type of combined oral contraceptive formulation [139, 140] or to any histologic type of ovarian cancer, although the inverse relation is less consistent for mucinous cancers [11, 13, 16, 141]. There are few epidemiologic studies that have evaluated progestin-only contraceptives, mostly due to the rarity of this exposure, but the existing data suggest they too lower risk of ovarian cancer [84, 132, 142].

Oral contraceptive use corresponds to the avoidance of approximately 3,000–5,000 ovarian cancer cases and 2,000–3,000 deaths per year in both Europe [20] and in North America [143]. The use of OCs therefore has implications for individual risk assessment and on a public health scale.

Few recent studies have examined methods of contraception other than oral contraceptives and tubal ligation. In a population-based case-control study of 902 epithelial OC/tubal/peritoneal cases and 1,800 controls, Ness and colleagues [124] found that ever use of an intrauterine device (IUD) was associated with lower risk of OC (adjusted OR=0.75, 95 % CI: 0.59–0.95). The benefit was evident with short duration of IUD use (≤ 4 years), but risk progressively increased with longer duration of IUD use (albeit nonsignificantly). The authors suggested that shorter use may reduce upper genital tract inflammation by killing sperm, while longer use may imply more insertions and greater risk of infection and inflammation. IUD use has previously been associated with an increased OC risk (RR=1.76, 95 % CI: 1.08–2.85) among women in the Nurses' Health Study [144]; however, most IUD use in their study occurred in the 1970s–1980s prior to the newer IUD formulations. Contrary to results from the Nurses' Health Study [144] in which spousal vasectomy was not associated with OC risk (multivariate adjusted OR=0.87, 95 % CI: 0.63–1.19), Ness and colleagues [124] observed vasectomy to be protective (adjusted OR=0.77, 95 % CI: 0.61–0.99). The authors [124] specu-

lated that vasectomy may confer a slight risk reduction from reduced exposure to sperm. Given that contraceptive methods are modifiable, these findings need to be replicated.

Hormone Replacement Therapy (HRT)

The benefit of oral contraceptives on OC risk is well established; however, the data on another exogenous hormone, HRT, is less clear. It has been postulated that HRT may reduce OC risk by decreasing the secretion of gonadotropins. However, the reduced levels are still above those of premenopausal women [145]. Conversely, postmenopausal HRT may increase OC risk due to increased estrogen-induced proliferation of ovarian cells [146].

Initial studies on the topic focused on unopposed estrogen therapy. In the collaborative reanalysis of 12 US case-control studies, no association was identified with duration of HRT use in either hospital-based (OR=0.90 for a 5-year increment of use, $p=0.37$) or population-based (OR=1.10 for a 5-year increment of use, $p=0.21$) studies [66]. Several case-control studies [147, 148], cohort studies, [149] and meta-analyses [150, 151] found no association with duration of use, although two have observed either a significant increase or a suggestive trend towards increased risk [13, 152]. Data from recent studies, including four meta-analyses, now indicate an increased OC risk for ever users of HRT [153–156]. Furthermore, several prospective studies have found that longer durations of HRT use are associated with OC risk or death [157–160]. For example, in the Nurses' Health Study cohort, both current and past HRT users of 5 or more years had a significantly higher risk for OC than never users current users (RR=1.41, 95 % CI: 1.07–1.86) and past users (RR=1.52, 95 % CI: 1.01–2.27) [161]. Based on their statistical modeling, the authors concluded that the elevated risk appeared to be driven largely by duration rather than by status of use. Additionally, in the UK Million Women Study [153], 2,273 incident ovarian cancers were observed among 948,576 postmenopausal women who did not have a prior cancer history or a bilateral oophorectomy. For current users of HRT, incidence of OC increased with increasing duration of use, but did not differ

significantly by type of preparation used and its constituents or mode of administration.

Only recently have studies had sufficient statistical power to evaluate associations between combined estrogen and progestin use and OC risk. The effects of unopposed estrogen therapy (ET) are thought to be more detrimental to the ovaries than estrogen plus progestin (EPT) [162]. It is postulated that progestins promote apoptosis, while estrogen promotes proliferation of ovarian epithelial cells [162]. Most studies that investigated the association between EPT use and OC risk have found no association or a weak association [141, 153, 154, 156, 159, 161–164]; however, not all studies support a protective role for EPT. A few prospective studies [153, 158, 165] and meta-analysis [155] have reported a small increased risk for EPT users. In support of a weaker association for EPT, a recent meta-analysis of 14 population-based studies found that ET is associated with an increased risk of OC (RR=1.22 for a 5-year increment of use, $p<0.0001$); however, the risk among women who used EPT was attenuated (RR=1.10 for a 5-year increment of use, $p=0.001$) [154]. The authors suggest that the addition of progestin mitigates the effect of estrogen, because the increased risk of OC among EPT users was statistically significantly lower than the risk among ET users, $p=0.004$ [154]. However, a large nationwide prospective cohort study of Danish women observed an increased risk both for ET users (RR=1.31, 95 % CI: 1.11–1.54) and for EPT users (RR=1.50, 95 % CI: 1.34–1.68) [165].

A recent cohort study investigated the association between HRT use and obesity on OC risk [166]. Among HRT nonusers, weight gain, waist circumference, and waist-to-hip ratio but not BMI increased the risk of OC [166]. HRT use of more than 5 years increased OC risk, but risk was not further increased for women who were overweight and used HRT. For example, while substantial weight gain (greater than 40 lbs) and HRT use of more than 5 years individually increased the risk of OC, the joint effect did not further increase the risk, which may imply a threshold effect [166]. Some studies have pointed to an

increased risk only for certain histologic subtypes of OC. For example, the Nurses' Health Study cohort observed that the association with ET was slightly stronger for endometrioid tumors, which is consistent with other studies [17, 148, 167]. A link between ET and the development of endometrioid ovarian tumors is biologically plausible because endometrioid tumors are histologically similar to endometrial tissue [168], and ET use increases the risk of endometrial cancer [146]. However, although risks associated with HRT use varied significantly according to tumor histology ($p<0.0001$) in the UK Million Women Study [153], the relative risk for current versus never users of HRT was greater for serous than for mucinous, endometrioid, or clear cell tumors (1.53 (1.31–1.79), 0.72 (0.52–1.00), 1.05 (0.77–1.43), or 0.77 (0.48–1.23), respectively).

It can be concluded from the available evidence that if an association exists between HRT use and OC, the magnitude is probably moderate, but women should be counseled about the potential increase in risk with long-term use of unopposed estrogen. Evidence suggests that the OC risk with ET alone is higher than the risk associated with EPT. Since many women are exposed to HRT several years before the peak age-specific incidence of OC, even a small change in risk may have a significant impact on disease rates at the population level.

Anthropometric Factors

The previous sections highlighting the importance of hormonal factors raise questions about other potential influences on circulating levels of estrogens. One area of great interest is body mass index (BMI), calculated as weight in kilograms divided by height in meters squared. In postmenopausal women the predominant source of circulating estrogens is aromatization of androgens in adipose tissue [52, 169]. The compelling role of obesity in the pathogenesis of hormone-related cancers has prompted research on the potential association with OC [170]. Despite a growing body of literature, the association between BMI and OC risk remains unresolved.

A 2007 meta-analysis of 28 population based studies reported an increased risk of OC for overweight women (BMI of 25–29.9 kg/m²) and obese women (BMI ≥ 30 kg/m²) compared with normal weight (BMI of 18.5–24.9 kg/m²), pooled RR=1.2 and 1.3, respectively [171]. A more recent report from the EPIC study obtained very similar results [172]. In a 2008 analysis of 12 prospective cohort studies, an increased OC risk was seen among premenopausal obese women compared to normal weight women (RR=1.72, 95 % CI: 1.02–2.89); however, this increased risk was not apparent among postmenopausal women (RR=1.07, 95 % CI: 0.87–1.33) [173].

Recent studies have investigated the relationship between obesity and OC risk stratified by hormone therapy (HT) use [166, 172, 174, 175]. In the EPIC study, higher BMI (HR per 2 kg/m²=1.05, 95 % CI: 1.01–1.08) and hip circumference (highest vs lowest quartile), RR=1.3 (95 % CI: 1.04–1.70), were associated with increased OC risk, [172] but waist circumference and waist-to-hip ratio (WHR) were not. In the Nurses' Health Study (NHS), greater hip circumference was a risk factor among postmenopausal women, but WHR, waist circumference, and BMI were not [175]. The results for BMI did not differ by hormone therapy use in the NHS or EPIC study. In contrast, two studies found an increased OC risk among obese never HT users (RR 1.8, 95 % CI: 1.2–2.8) [174] and an increased risk for greater weight gain since age 18 (RR=1.8, 95 % CI: 1.0–3.0 for ≥40 lbs. vs stable weight), a larger waist circumference (RR=1.8, 95 % CI: 1.1–3.0 for ≥35 vs <35 in.), and a larger waist-to-height ratio (RR=1.8, 95 % CI: 1.1–3.1 for ≥35 vs <35 in.) [166].

It is hypothesized that different histologic subtypes of OC have different etiologies, and thus, recent studies have investigated the association between obesity and subtypes of epithelial OC. An increased risk for OC has been observed between WHR and risk of mucinous tumors (HR per 0.05 unit increment=1.19, 95 % CI: 1.02–1.38), but not with serous, endometrioid, or clear cell tumors [172]. The large prospective NIH-AARP Diet and Health Study reported that endometrioid OC risk was increased among

obese women (RR=1.64, 95 % CI: 1.00–2.70), but no association was seen for serous OC [176]. Similarly, in the NHS, obesity was associated with increased endometrioid risk [17]; however, in a systematic review only the pooled analysis and one case-control study found BMI to be associated with an increased risk of endometrioid OC [171]. In another pooled analysis, no association between BMI and risk of endometrioid, mucinous, or serous tumors was evident [173].

The findings to date suggest BMI may confer a slight increased risk of OC, but considering adiposity is a modifiable risk factor, future studies on different anthropometric measures are warranted. Additionally, the possible relationship between OC risk and BMI among women who have never used HT should be investigated in future studies.

Diet and Nutrition

The previous section on anthropometric factors raises questions about the role of dietary factors, especially energy intake (balance) in the etiology of OC. Ecological studies have generated a number of hypotheses about the association between diet and OC risk [177]. Despite numerous analytical epidemiologic studies on various aspects of diet, the findings for most exposures remain inconsistent. The notable exception is intake of vegetables, for which the evidence that higher intakes are associated with lower risk is emerging [177], and to a certain extent also for consumption of whole grain foods and low-fat milk. However, the association between specific fats and oils, fish and meats, and certain milk products is inconsistent and awaits further investigation before firm conclusions can be made. Recent epidemiologic studies on meat consumption and OC do not provide further clarification [178–180]; however, a large prospective study found that women in the highest intake quartile of dietary nitrate had an increased risk of OC (HR=1.31, 95 % CI: 1.01–1.68, and *p*-value for trend=0.02). Similarly, the association between coffee intake and OC risk has been inconclusive to date, and a recent systematic review found no significant

associations [72, 76, 181–185]. Although several studies including a recent systematic review noted a trend towards lower risk among tea drinkers, the findings remain inconsistent [181, 186, 187].

Since vitamin D levels are derived in part from our diet or dietary supplements, the literature on vitamin D is included in this section, even though the main source is production in the skin from sun exposure [188]. Vitamin D is converted to 25-hydroxyvitamin (25(OH)D) in the liver and further metabolized to the active form in the kidney, 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}_3$) [188]. Experimental studies have shown that $1,25(\text{OH})_2\text{D}_3$ inhibits cell proliferation in OC cell lines and induces apoptosis [189]. However, a recent systematic review of the epidemiologic literature concluded that there is no consistent or strong evidence that vitamin D decreases OC risk [190]. A meta-analysis of ten longitudinal studies reached a similar conclusion [191]. Although seven of the ten studies found a 17 % reduced risk of OC with increasing 25(OH)D levels, the pooled estimate was not statistically significant ($\text{RR}=0.83$, 95 % CI: 0.63–1.08) [191]. There is some evidence that the beneficial effect of vitamin D may be more pronounced among overweight or obese women [189, 192], perhaps reflecting differential bioavailability of circulating 25(OH)D levels [189].

Exercise and Physical Activity

The potential general health benefits of exercise are well established, and a specific effect on OC might be expected, at least indirectly, through exercise effects on reduction of adipose tissue (and therefore estrogen levels), lower ovulation frequency, and reduced chronic inflammation [193]. To date, 23 epidemiologic studies have investigated the association between physical activity and OC risk, including ten prospective cohort studies [194–203], two historical cohort studies [204, 205], eight population-based case-control studies [183, 206–212], and three hospital-based case-control studies [213–215]. Results are not entirely consistent, but a 2007 meta-analysis estimated a nearly 20 % lower risk

for the most active women compared to the least active (pooled relative risk=0.81, 95 % CI: 0.72–0.92) [210]. Most studies that measured physical activity across the lifespan reported consistent null findings [200, 201, 208, 210] or risk reductions [183, 207, 209, 213] in each age period; however, one study [211] reported that strenuous recreational activity early in life may increase OC risk. Similarly, prolonged sedentary behavior, greater than 6 h compared to less than 3 h, was associated with an increased risk of OC ($\text{HR}=1.55$; 95 % CI: 1.08, 2.22; p for trend=0.01) [200]. An increased risk of OC was also found for high level versus low level of total sitting duration, $\text{OR}=1.77$ (95 % CI: 1.0–3.1) [216]. Because each OC subtype has different clinical and morphological features, the association between OC risk and physical activity may vary by histologic type [209, 212], but there is insufficient data to draw firm conclusions. Even though questions remain unanswered regarding the relationship between exercise and physical activity and OC risk, when considering the additional benefits of exercise on weight control, bone density, and heart disease, the promotion of regular activity to women should be encouraged.

Other Lifestyle and Environmental Factors

Cigarette Smoking

The majority of early reports concluded that smoking was not associated with an increased risk of OC [85, 184, 217, 218]. Based on results from more contemporary studies, this may have been because analyses were not stratified by histologic subtype. In fact, smoking appears to increase the risk for invasive mucinous tumors in a dose-response manner, but not other subtypes [12, 15, 219]. In 2006, a systematic literature review and meta-analysis [220] concluded that there is a doubling of risk of mucinous OC among current smokers compared to never smokers (summary RR 2.1, 95 % CI: 1.7–2.7), but no increased risk of serous (1.0, 95 % CI: 0.8–1.2) or endometrioid (0.8, 95 % CI: 0.6–1.1) cancers, and a significant risk reduction for clear cell

cancers (0.6, 95 % CI: 0.3–0.9). The risk of mucinous cancer increased in a dose-response relationship but returned to that of never smokers within 20–30 years of stopping smoking. A population-based study of 812 women with OC diagnosed in Washington State and 1,313 controls published since that meta-analysis also showed that the incidence of borderline and invasive mucinous ovarian tumors was increased among women with a cigarette smoking history (OR = 1.8; 95 % CI: 1.2–2.9 and 0.8–4.3, respectively) [221]. The risk of invasive serous cancers was slightly increased among those who had smoked within the previous 15 years (OR = 1.4, 95 % CI: 1.1–1.9), but the risk for endometrioid and clear cell tumors was not elevated among smokers [221]. Histologically, mucinous ovarian tumors resemble mucinous gastrointestinal cancers, some of which (pancreatic cancer, gastric cancer) have been classified as smoking-related cancers [220]. Collectively, these findings suggest that risk of OC is one more reason to avoid cigarette smoking.

Alcohol Consumption

Alcohol consumption, a common and modifiable exposure, has been investigated as a possible cause of OC in numerous case-control and cohort studies with conflicting results. Most have observed null associations [67, 85, 183, 184, 222, 223], but there is an equal number that have found increased risk [72, 224, 225] and decreased risk [226–228]. There have been efforts to resolve the observed inconsistency by quantifying risk by the type of alcohol consumed (wine, beer, or alcohol) [225, 226] or histologic subtype of the tumor [225, 226, 228]. In a large population-based case-control study [229], consumption of beer (not liquor or wine) during early adulthood (20–30 years of age) was associated with a moderately increased risk of invasive OC, with the association limited to serous tumors (OR 1.52, 95 % CI: 1.01–2.30), though results for other histologic subtypes were based on sparse data. This risk was associated with regular consumption (one or more drinks per day), and there was no evidence of a dose-response relationship. Data from the Netherlands Cohort Study on Diet and

Cancer found no association between alcohol consumption in the form of wine, beer, or liquor and OC risk [230]. A recently published pooled analysis of 10 cohort studies that included over 500,000 women and 2001 incident OC cases also found no association between total alcohol intake (pooled multivariate RR = 1.12, 95 % CI: 0.86–1.44 comparing ≥ 30 –0 g day of alcohol) or alcohol intake from wine, beer, or spirits and OC [231]. There was no association (OR = 1.13, 95 % CI: 0.92–1.38; random effects) between wine consumption and OC risk in a recent meta-analysis of 10 studies (3 cohort and 7 case-control studies) with 135,871 women, including 65,578 wine drinkers [232]. Based on these data, it seems reasonable to conclude that if alcohol intake does influence risk of OC, the magnitude is small and possibly limited to particular histologic subtypes.

Occupational Exposures

Assessment of occupational risk factors for OC has been challenging due to a lack of well-designed epidemiologic studies adequately powered to detect associations; however, there is some evidence for excess risk among women employed in dry cleaning, telecommunications, paper packaging, and textile industries [233, 234], perhaps implicating exposures to organic dusts, aromatic amines, and hydrocarbons.

Asbestos and Talcum Powder

Both human [235, 236] and animal studies [237] have found asbestos fibers in the ovaries. The link between asbestos exposure and OC is less firmly established, in part due to small numbers of women who have been exposed to asbestos and disease misclassification (i.e., peritoneal mesothelioma, an asbestos-related disease, is often misdiagnosed as OC on death certificates). A recent systematic review and meta-analysis of fourteen cohort and two case-control studies [238] noted a statistically significant excess mortality in four of the cohort studies, all of which relied on death certificates for reports of the outcome. After including all studies in the meta-analysis, there was a 75 % excess risk of OC in women who had been exposed to asbestos

(effect size = 1.75 (95 % CI: 1.45–2.10)). However, the association was attenuated (effect size = 1.29 (95 % CI: 0.97–1.73)) among studies that examined cancer incidence based upon pathologically confirmed OCs [238]. Despite the lack of consistency, the International Agency for Research on Cancer (IARC) has declared that evidence is “sufficient” in humans that exposure to asbestos causes OC [239].

Similar to asbestos, talcum powder is a silicate that has been studied extensively in relation to cancer risk. A meta-analysis of 16 studies reported an approximately 30 % increase in risk of OC with regular genital exposure to talc [240], and more recent studies suggest that women with certain variants in glutathione S-transferase M1 (*GSTM1*) and/or glutathione S-transferase T1 (*GSTT1*) may have a higher risk of OC associated with talc use [241]. However, as summarized by Muscat and Huncharek [242], mechanistic, pathology, and animal studies do not support evidence for the carcinogenicity of talc on the ovarian epithelium.

Asthma

Epidemiologic studies have identified inverse associations between the presence of allergies and the development of certain cancers [243]. Using the presence of asthma as an indicator for an allergy, El Masri and colleagues [244] conducted a hospital-based study of 1,582 cases and two large series of controls with bone fractures ($n=4,744$) and acute myocardial infarction ($n=21,830$). After adjusting for age, race-ethnicity, Medicaid status, obesity, and smoking, cases were 30 % less likely than controls with fractures to be asthmatics (adjusted OR = 0.70, 95 % CI: 0.49–0.99). Similarly, when compared to controls with acute myocardial infarction, cases were less likely to have asthma (adjusted OR = 0.62, 95 % CI: 0.45–0.87). These intriguing findings merit replication efforts.

Drug Use

Several recent prospective studies [245, 246] have investigated the association between aspirin and nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) and OC incidence. Using data

from the Nurses’ Health Study and the Nurses’ Health Study II, Pinheiro and colleagues [245] found that regular use of aspirin and NSAIDs was associated with hazard ratios of 1.11 (95 % CI: 0.92–1.33) and 0.81 (95 % CI: 0.64–1.01), respectively. No dose-response relationship with increased frequency or duration of use was observed, and results did not differ when stratifying by tumor histology [245]. Prizment and colleagues [246] investigated these drugs using data from a prospective cohort of approximately 20,000 women who were part of the Iowa Women’s Health Study. Compared to women who reported no use of aspirin, the relative risks of OC for those who used aspirin <2, 2–5 times, and ≥ 6 times per week were 0.83, 0.77, and 0.61, respectively (p trend = 0.04). No association was observed between NSAID use and OC risk.

As summarized recently by Li and colleagues [247], a growing body of evidence supports a role for the antidiabetic agent, metformin, in cancer prevention and treatment. To evaluate the association between use of metformin or other antidiabetic drugs and OC risk, a case-control study including 1,611 incident OC cases was performed using the UK-based General Practice Research Database [248]. Long-term use (≥ 30 prescriptions) of metformin (and not sulfonylureas) was associated with a trend towards reduced OC risk (OR = 0.61, 95 % CI: 0.30–1.25), although results were not statistically significant. Further large-scale studies are needed before initiating prospective trials to investigate metformin as a chemopreventive (or therapeutic) agent.

Summary and Conclusions

Ovarian cancer is a leading cause of cancer incidence and mortality among women worldwide. This chapter describes the magnitude of the problem and summarizes epidemiologic studies that have provided clues on factors that may increase and decrease risk of this heterogeneous disease. Although many of the risk factors in Table 1.2 cannot be modified, reflecting the contribution of genetics and unavoidable exposures, a number of others can be altered. Increasing parity and oral