Advances in Diagnosis and Management of Ovarian Cancer

Samir A. Farghaly
Editor

Second Edition

Springer

Advances in Diagnosis and Management of Ovarian Cancer

Samir A. Farghaly
Editor

Advances in Diagnosis and Management of Ovarian Cancer

Second Edition

Springer

Editor
Samir A. Farghaly
Department of Obstetrics and Gynecology
Joan and Sanford Weill Cornell University
Medical Center - New York-Presbyterian Hospital
and Sandra and Edward Meyer Cancer Center- Cornell University
New York, NY, USA

ISBN 978-3-031-09168-1 ISBN 978-3-031-09169-8 (eBook)
https://doi.org/10.1007/978-3-031-09169-8

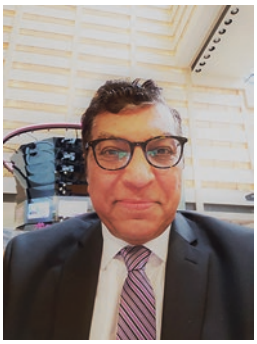
© Springer Nature Switzerland AG 2022
This work is subject to copyright. All rights are reserved by the Publisher, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilms or in any other physical way, and transmission or information storage and retrieval, electronic adaptation, computer software, or by similar or dissimilar methodology now known or hereafter developed.
The use of general descriptive names, registered names, trademarks, service marks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.
The publisher, the authors, and the editors are safe to assume that the advice and information in this book are believed to be true and accurate at the date of publication. Neither the publisher nor the authors or the editors give a warranty, expressed or implied, with respect to the material contained herein or for any errors or omissions that may have been made. The publisher remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

This book is dedicated to my beloved children Raied and Tamer, to the memory of my mother Amina, to my father Aly who had a great influence on me, and to my academic and professional medical career. Also, to my sisters: Soraya, Nadia and their families, to my late siblings: Nabil, Rafat, Magdy and to their present families in addition to my late nephew, Islam.

Samir A. Farghaly, MD, PhD
New York, NY, USA

Preface



Globally, the numbers of ovarian cancer new cases were about 300,000 and 200,000 deaths in 2018. In 2021, about 21,410 new cases of ovarian cancer were diagnosed and 13,770 women died of ovarian cancer in the USA. The ovarian cancer statistics for incidence indicate that 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 non-melanoma 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 aging, being 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 targeted molecular 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, and open surgical, minimally invasive surgical and targeted molecular therapy for patients with hereditary and non-hereditary ovarian cancer. The importance of updated knowledge of the epidemiology of ovarian cancer as it

affects primary prevention, early detection, and possibly therapeutic strategies are discussed in Chap. 1. The current screening and early detection are detailed in Chap. 2. The importance of ovarian cancer biomarkers and its clinical relevance are discussed in Chap. 3. The diagnosis and management of hereditary ovarian cancer are discussed in Chap. 4. The origin, histopathologic, and molecular genetic aspects of ovarian cancer are detailed in Chap. 5. The current management of patients with early-stage ovarian cancer is detailed in Chap. 6. The management of advanced stage ovarian cancer is discussed in Chap. 7. Detailed management of recurrent ovarian cancer is shown in Chap. 8. An extensive overview of chemotherapy for ovarian cancer patients is discussed in Chap. 9. Special reference to management of advanced ovarian cancer with peritoneal metastases is detailed in Chap. 10. Targeted molecular therapy for patients with ovarian cancer is thoroughly discussed in Chap. 11. The recent advances in diagnosis and management of ovarian neoplasms in the pediatric female population of less than 17 years old is discussed in Chap. 12. 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. 13.

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, United Kingdom, Australia, and Turkey who have authored its contents.

I would like to thank Ms. Pinky Sathishkumar, project coordinator of this book, and Ms. Samantha Lonuzzi, clinical medicine editor at the book publishers Springer Nature for their efficiency and valuable help in the process of development, editing, and publishing of this book

New York, NY, USA Samir A. Farghaly

Contents

Contributors

Rachel Campbell, BPsych, MSc (ClinPsych), PhD University of Sydney, Faculty of Science, School of Psychology, Sydney, NSW, Australia

Mary Dandulakis, MD Department of Obstetrics, Gynecology, & Reproductive Sciences, University of Maryland School of Medicine, Baltimore, MD, USA

James Dilley, MRCOG Department of Gynaecological Oncology, The Royal London Hospital, St. Bartholomew's NHS Trust, Whitechapel, London, UK

Mona El-Bahrawy, MBBCh, MSc, PhD, FRCPath Section of Pathology, Faculty of Medicine, Imperial College London, London, UK

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 Division of Pediatric Surgery, Palm Beach Children's Hospital at St Mary's Medical Center, West Palm Beach, FL, USA

Department of Surgery, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA

Angela George, MB ChB, MD, FRACP Gynaecology Unit, The Royal Marsden NHS Foundation Trust, London, UK

Cancer Genetics Unit, The Royal Marsden NHS Foundation Trust, London, UK

Ece Gumusoglu-Acar, MSc Faculty of Science, Molecular Biology and Genetics, Istanbul University, Istanbul, Turkey

Tuba Gunel, PhD Faculty of Science, Molecular Biology and Genetics, Istanbul University, Istanbul, Turkey

Madeleine T. King, BSc (hons), PgDip MedStats, PhD University of Sydney, Faculty of Science, School of Psychology, Sydney, NSW, Australia

Kylie Klein, MD Department of Obstetrics, Gynecology, & Reproductive Sciences, University of Maryland School of Medicine, Baltimore, MD, USA

Fani Kokka, MRCOG East Kent Gynaecologic Oncology Centre, Queen Elizabeth The Queen Mother Hospital, Kent, UK

Ioannis C. Kotsopoulos, MD, MPhil, PhD Gynaecological Oncology Department, University College London Hospital, London, UK

Alexandra Lawrence, MD, MRCOG Department of Gynaecological Oncology, The Royal London Hospital, St. Bartholomew's NHS Trust, Whitechapel, London, UK

Yeh Chen Lee, MBBS, BMedSci, FRACP NHMRC Clinical Trials Centre, Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

Prince of Wales Hospital, Sydney, NSW, Australia

Monica Levine, MD The James Cancer Hospital and Solove Research Institute, The Ohio State University College of Medicine, Columbus, OH, USA

Linda Mileshkin, MBBS, MD, FRACP, MBioeth Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Rowan E. Miller, MA, MBBS, MRCP, PhD Medical Oncology Department, University College London Hospital, London, UK

Timothy A. Mould, MD, FRCOG, MBBS, MA, DM Gynaecological Oncology Department, University College London Hospital, London, UK

R. Wendel Naumann, MD Levine Cancer Institute, Atrium Health, Charlotte, NC, USA

Adeola Olaitan, MD, FRCOG University College London NHS Trust, London, UK

Dana M. Roque, MD Department of Obstetrics, Gynecology, & Reproductive Sciences, University of Maryland School of Medicine, Baltimore, MD, USA

Division of Gynecologic Oncology, University of Maryland School of Medicine, Baltimore, MD, USA

Claudia Rutherford, BPsych, PhD University of Sydney, Faculty of Science, School of Psychology, Sydney, NSW, Australia

Paul H. Sugarbaker, MD Program in Peritoneal Surface Malignancy, Washington Cancer Institute, Washington Hospital Center, Washington, DC, USA

Margaret-Ann Tait, BAS (Psych), MSc (CoachPsych) University of Sydney, Faculty of Science, School of Psychology, Sydney, NSW, Australia

Ovarian Cancer Epidemiology

1

Fani Kokka and Adeola Olaitan

Incidence and Geographical Distribution of Ovarian Cancer

Women make up 49.5% of the world population but they form a higher proportion of those over 60 years of age in whom cancer is most likely to occur. Cancer is the leading cause of death in women worldwide, both in well-resourced and poorly resourced countries [1]. Ovarian cancer is the 8th most common cancer in women and the 18th most common overall. Worldwide there were just under 300,000 ovarian cancer cases in 2018 [2]. It accounts for 4% of global cancer incidence [3].

There are geographical variations in the frequency of ovarian cancer. Ovarian cancer incidence rates are greater in high than in middle- to low-income countries. Around the world, age-standardised incidence rates range from more than 11 per 100,000 women in Central and Eastern Europe to less than 5 per 100,000 in parts of Africa. Serbia had the highest incidence rate in 2018, while the UK ranked 19th in age-standardised rates [3].

F. Kokka, MRCOG (✉)
East Kent Gynaecologic Oncology Centre, Queen Elizabeth The Queen Mother Hospital, Kent, UK
e-mail: fani.kokka@nhs.net

A. Olaitan, MD, FRCOG
University College London NHS Trust, London, UK
e-mail: adeola.olaitan@nhs.net

The number of women being diagnosed with ovarian cancer is likely to see a significant increase over the next two decades, according to a new study. The World Ovarian Cancer Coalition, a group of patient organisations, has published its 2018 Every Woman Study, which has collated data from 1000 women in 39 countries, making it the most comprehensive study ever of the global impact of ovarian cancer [4]. It predicted that ovarian cancer incidence will rise by nearly 55% in the next 20 years unless urgent action is taken, with UK incidence rates projected to increase by 15% over this period.

Types of Ovarian Cancer

Ovarian cancers are a heterogenous group (Table 1.1). The most common ovarian cancers are known as epithelial ovarian cancers of which high-grade serous cancer is the commonest. Further discussions refer to epithelial tumours except otherwise specified.

Recent data suggest that there are two types of epithelial ovarian cancer [5]: Type 1 cancers include low-grade serous, endometrioid, clear cell, and mucinous types. They tend to grow locally, metastasize late, and behave in a more indolent fashion. They are believed to arise from inclusion cysts or in implants of the ovarian surface epithelium. The endometrioid and clear cell ovarian cancer appear to arise in association with

© Springer Nature Switzerland AG 2022

S. A. Farghaly (ed.), *Advances in Diagnosis and Management of Ovarian Cancer*,
https://doi.org/10.1007/978-3-031-09169-8_1

Table 1.1 Ovarian cancer subtypes

Type	Frequency (%)	Subtype
Epithelial	90	Serous 52%
		Endometrioid 10%
		Mucinous 6%
		Clear cell 6%
Germ cell	3	Dysgerminoma
		Embryonal carcinoma
		Endodermal sinus tumour (yolk sac)
		Choriocarcinoma
		Malignant teratoma
Sex cord/ stromal	2	Granulosa cell tumours
		Sertoli–Leydig tumours

endometriosis, suggesting that the endometrial lining, via retrograde menstruation, is the source for many type 1 cancers. They are associated with KRAS, ARID1A, PIK3CA, PTEN, and BRAF mutations. Type 2 cancers include high-grade serous, carcinosarcomas, and undifferentiated carcinomas. They are highly aggressive and they generally present at advanced stage. They are believed to arise in the fallopian tube or from the ovarian epithelium. Observational studies suggest that the majority of type 2 ovarian cancers originate as high-grade lesions in the distal end of the fallopian tube; they transform to cancerous cells that seed to the ovary and rapidly spread through the peritoneal cavity. They are associated with TP53 mutations.

Risk Factors of Ovarian Cancer

The epidemiology may, to an extent, reflect the risk factors for ovarian cancer. Because of its heterogeneity, epithelial ovarian cancer has been associated with different risk factors for the various histopathological types [6]. There is a broad spectrum of evidence suggesting sufficient or convincing data for some of the risk factors, and there are limited or probable data for others. The best quality data regarding risk factors for epithelial ovarian cancer come from two large prospective studies: (1) The United States (US) Nurses' Health Study that has followed >200,000 women, with 924 cases of epithelial ovarian cancer to date, and (2) The European Prospective Investigation into Cancer and Nutrition (EPIC) that has followed >300,000 women, with 878 cases of epithelial ovarian cancer to date [7].

Age

Older age is the main risk factor for epithelial ovarian cancer as over 50% of cases occur in postmenopausal women. In the UK in 2013–2015, on average each year more than a quarter (28%) of new cases were in females aged 75 and over [8]. Age-specific incidence rates rise steadily from around age 30–34 and more steeply from around age 45–49, with a sharp drop in the oldest age groups. The highest rates are in the 75–79 age group [6].

Family History

Family history is one of the strongest risk factors for ovarian cancer. Inherited genetics appear to be more significant than the environmental and lifestyle circumstances [9]. They cause around 5–15% of cases of ovarian cancer [6]. Personal history or family history of breast cancer and family history of a first-degree relative with ovarian cancer have been considered as risk factors for ovarian cancer; however, BRCA gene mutations appear to account for most of this increased risk [7]. General population estimated risk of carrying BRCA mutations varies between 1:300 and 1:800, and in certain groups like the Ashkenazi Jews it is estimated to be 1:40 individuals [9]. Certain populations are associated with a higher incidence of BRCA mutations. For example, Ashkenazi Jewish ancestry (those of European origin) have higher rates of carriage than in Sephardic Jews (those of African and Asian descent) and the rest of the general population [10].

The first breast cancer gene to be discovered is called BRCA1, and inherited germline mutations in BRCA1 increase the risk of breast, ovarian, uterus, cervix, pancreatic, and possibly prostate cancer [11]. Approximately 1.5% of the Ashkenazi Jewish population carries an inherited mutation in the BRCA1 gene.

The second breast cancer gene is called BRCA2. Since its discovery in December of 1995, researchers have come to a better understanding of the role of the BRCA2 gene in the development of cancer. Every cell in our body has two copies of BRCA2. One is inherited from each parent. An ancestor of Eastern European Jews, approximately 29 generations ago, developed a defect in the DNA coding for the BRCA2 gene. This DNA defect, known as the 6174delT mutation, has been passed from generation to generation. As a result, 1% of all Ashkenazi Jews living now inherit a defective copy of one of their BRCA2 genes. Carriers of the BRCA2 mutation are at increased risk of developing breast, ovarian, prostate, and pancreatic cancer [11].

Patients with BRCA1 gene mutation have a 39–46% overall risk of developing ovarian cancer by the age of 70, and patients with BRCA2 gene mutation have a 10–27% overall risk of developing ovarian cancer by the age of 70 [9]. These inherited cancers are most frequently of the high-grade serous subtype, which constitutes approximately 60% of epithelial ovarian cancers [9]. In addition, the BRCA gene mutation is the most established risk factor for fallopian tube and peritoneal cancer carcinoma [7]. BRCA mutation carriers typically present with ovarian cancer at a younger age than those with sporadic cancers. Risk-reducing surgery for known BRCA carriers with bilateral salpingo-oophorectomy has been successful in reducing epithelial ovarian cancer mortality [9].

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer syndrome, includes multiple adenocarcinomas and is associated with colon cancer, endometrial cancer, breast cancer, and other malignancies of the gastrointestinal and genitourinary systems, including the risk of ovarian cancer. Women with Lynch syndrome account for 1% of ovarian cancer. The lifetime risk of ovarian cancer in women with Lynch syndrome is 3–14% compared with 1.5% in the general population [7]. The mutations associated with this syndrome are MSH2, MLH1, PMS1, and PMS2 [12]. The most common subtypes of ovarian cancer associated with Lynch syndrome are the endometrioid and the clear cell type [9]. The typical age of diagnosis of ovarian cancer in women with Lynch syndrome is 43–50 years old [7], which is younger age than the other women, at around 60 years old.

Peutz-Jeghers syndrome, which is an autosomal dominant genetic disorder associated with benign hamartomatous polyps in the gastrointestinal tract and hyperpigmented macules on the lips and oral mucosa, has been associated with significant ovarian cancer risk from a meta-analysis that has shown that 21% of women with this syndrome develop ovarian cancer aged 15–64 [6].

All the known susceptibility genes that we currently know they are associated with ovarian cancer account for less than half of the heritable causes of this disease, suggesting there are more mutations to be discovered [9].

Reproductive Factors

Ovarian cancer risk is associated with factors affecting ovulation. Decreased risk of ovarian cancer is associated with suppression of ovulation. Early menarche and/or late menopause are associated with higher risk of ovarian cancer [13]. Multiparous women are considered to have 30–60% lower risk for ovarian cancer compared with nulliparous women [14]. Infertility, especially unexplained infertility [15], is a risk factor for epithelial ovarian cancer, but ovulation induction for treatment of infertility does not appear to increase this risk [7]. Ovarian cancer risk is 24–30% lower in women who have ever breastfed versus those who have never breastfed [6]. These risk factors may cast some light on the geographical variations as while fecundity rates have fallen in Europe and North America, there remain high rates of childbirth in Asia and Africa [16].

Exogenous Hormones

The Oral Contraceptive Pill

The oral contraceptive pill reduces the risk of ovarian cancer compared to never-users. The risk decreases further with longer use of the oral contraceptive pill [13, 17].

Hormone Replacement Therapy

Hormone replacement therapy (HRT) has been associated with ovarian cancer in a number of studies [13, 18]; however, the absolute risk appears to be small [7]. Level 2 evidence from observational and cohort studies suggests that HRT is associated with increased risk of ovarian cancer; this risk appeared to be higher to current users compared to past users; unopposed oestrogen use for more than 10 years and increasing oestrogen dose with HRT is associated with increasing risk of ovarian cancer; however, the Women's Health Initiative (WHI) randomised control trial found no statistically significant increase in the risk of ovarian cancer with combined oestrogen-progestin therapy compared with placebo (42 versus 27 per 100,000 person-years; HR 1.6, 95% CI 0.8–3.2) [7]. A meta-analysis of 52 epidemiological studies has shown an increased risk of ovarian cancer in women who use HRT [18].

Medical Conditions

Endometriosis

Based on systematic review of observational studies, endometriosis is associated with increased risk of endometrioid and clear cell carcinoma [12, 13]. Compared to non-endometriosis-associated ovarian cancer, endometriosis-associated ovarian cancer is associated with decreased overall mortality and decreased incidence of serous carcinoma [13].

High BMI

High body mass index (BMI) appears to increase the risk of ovarian cancer [7]. Body mass ≥25 kg/m^2 at age 18 years was associated with increased risk of premenopausal ovarian cancer compared to BMI <20 kg/m^2 at age 18 years. However there were no significant differences in overall risk of ovarian cancer.

Diabetes

Ovarian cancer risk is higher in diabetics compared to non-diabetics [12].

Polycystic Ovarian Syndrome

Women with polycystic ovarian syndrome appear to have an elevated risk of ovarian cancer (OR 2.52, 95% CI, 1.08–5.89) based on a meta-analysis of eight case-control studies [7].

Other Factors

Genital Powder (Talcum Powder)

Systematic review of case-control studies showed that genital powder (talcum powder) is associated with increased risk of ovarian cancer [6, 19].

Smoking

Mucinous ovarian cancer has been associated with smoking [17, 20]. The association appears to be stronger with current users and with increased duration of smoking [6, 20].

Survival

Ovarian cancer carries a poor prognosis as most women present with advanced disease. The absence of an effective screening strategy and the non-specific nature of symptoms often mimic benign disease; mean women often do not become aware that there is a problem until other organs become affected. As a consequence, the majority of woman will have disease that has spread beyond the ovaries at diagnosis, making cure less likely. FIGO staging for ovarian cancer was revised in 2014 (Table 1.2).

Table 1.2 FIGO ovarian cancer staging (2014) [21]

Stage	Substage	
I	IA	Tumour limited to one ovary, capsule intact, no tumour on surface, negative washings
	IB	Tumour involves both ovaries otherwise like IA
	IC	Tumour limited to one or both ovaries
	IC1	Surgical spill
	IC2	Capsule rupture before surgery or tumour on ovarian surface
	IC3	Malignant cells in the ascites or peritoneal washings
II		Tumour involves one or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer
	IIA	Extension and/or implant on uterus and/or fallopian tubes
	IIB	Extension to other pelvic intraperitoneal tissues
III		Tumour involves one or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes
	IIIA	Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
	IIIA1	Positive retroperitoneal lymph nodes only
	IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
	IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
	IIIC	Macroscopic, extrapelvic, peritoneal metastasis >2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen
IV		Distant metastasis excluding peritoneal metastasis
	IVA	Pleural effusion with positive cytology
	IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

It is worth noting that the lowest survival prospects of all female cancers, with 5-year survival rates ranging between 30% and 50%. By comparison, more than 80% of women with breast cancer will survive for 5 years or more in many countries. Survival depends on the stage (Fig. 1.1) of disease as well as the cancer type, with high-grade serous cancer being associated with the highest mortality rates. There is also a geographical variation in survival, which reflects awareness and access to healthcare [22].

The UK has one of the lowest survival rates when compared to other European countries (Fig. 1.2) [6].

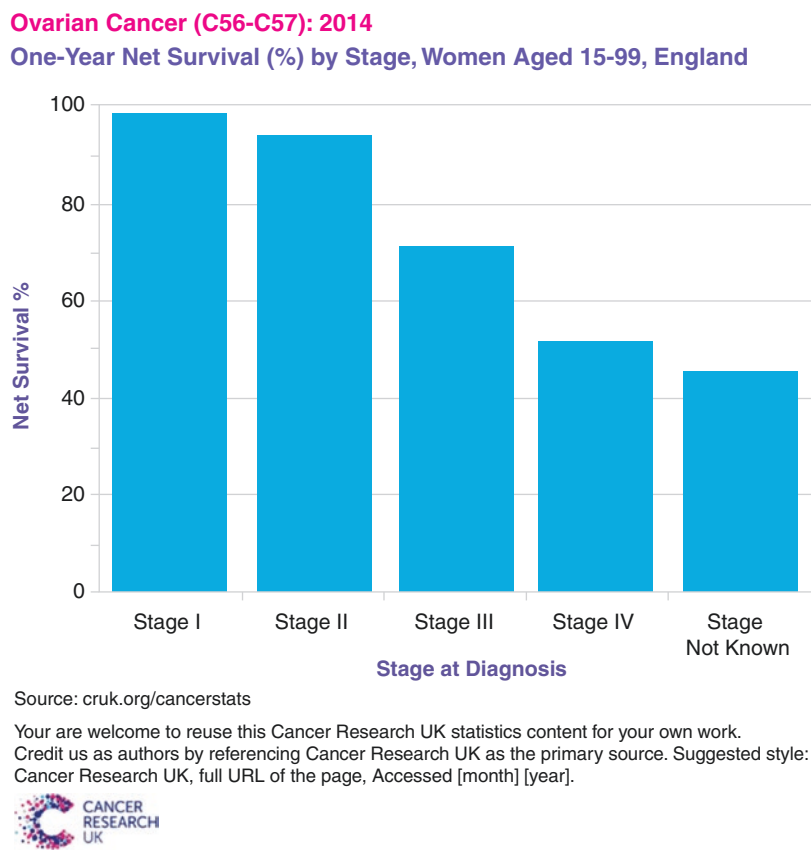


Fig. 1.1 Ovarian cancer survival by stage [6]

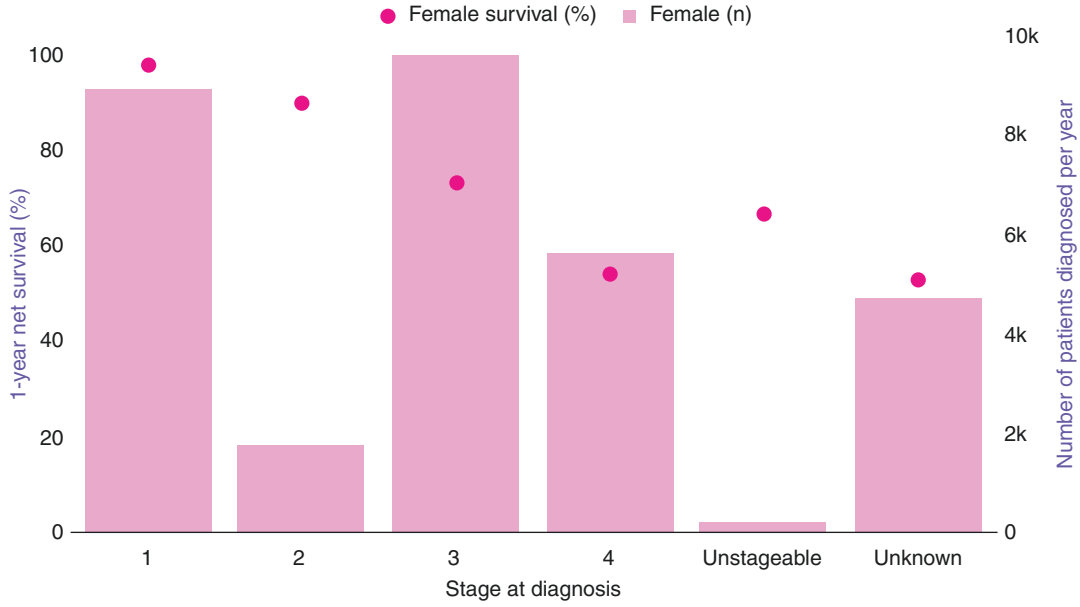


Fig. 1.2 Ovarian cancer 1-year net survival by stage, with incidence by stage (all data: adults diagnosed 2013–2017, followed up to 2018) [6]

Conclusion

Ovarian cancer is the eighth most common cancer in women and it accounts for 4% of global cancer incidence. Ovarian cancer incidence rates are greater in high than in middle- to low-income countries. The number of women being diagnosed with ovarian cancer is likely to see a significant increase over the next two decades. The most common ovarian cancers are known as epithelial ovarian cancers from which serous type is the most frequent. Epithelial ovarian cancer is a heterogeneous disease. The recognised risk factors do not account for all the types of the disease, but rather they are associated with different subtypes of ovarian cancer. Age, family history, and inherited genetics appear to be significant risk factors. In the majority of cases, ovarian cancer presents at advanced disease due to non-specific symptoms and no effective screening tests; because of this, it has poor survival range between 30% and 50%. Epidemiological evidence suggests that further studies are necessary to research the aetiology, identify screening methods, and offer treatment depending on the different subtypes of epithelial ovarian cancer.

References

1. United Nations Population Division. World population prospects, the 2015 revision. [cited 2016 October 14]. Available from: https://esa.un.org/unpd/wpp/.
2. Bray F, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Ferlay J, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359–86.
4. World Ovarian Cancer Coalition. Available from: https://worldovariancancercoalition.org/every-woman/.
5. Terada KY, Ahn HJ, Kessel B. Differences in risk for type 1 and type 2 ovarian cancer in a large cancer screening trial. J Gynecol Oncol. 2016;27(3):e25.
6. Cancer Research UK. Epithelial ovarian cancer. [cited 2019 March 26]; Content supplied by the world's largest charitable funder of cancer research, © Cancer Research UK [2002] All rights reserved. Available from: https://www.cancerresearchuk.org/about-cancer/ovarian-cancer/types/epithelial-ovarian-cancers.
7. DynaMed Plus. [cited 2019 March]; DynaMed Plus [Internet]. Ipswich, MA: EBSCO Information Services. 1995. Record No. T900705, Ovarian cancer; [updated 2018 Nov 30, cited 2019 March 29]. Available from: https://www.dynamed.com/topics/dmp~AN~T900705. Registration and login required.
8. Cancer Registration Statistics. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/previousReleases.
9. Mallen AR, Townsend MK, Tworoger SS. Risk factors for ovarian carcinoma. Hematol Oncol Clin North Am. 2018;32(6):891–902.
10. Walsh T, et al. Genetic predisposition to breast cancer due to mutations other than BRCA1 and BRCA2 founder alleles among Ashkenazi Jewish women. JAMA Oncol. 2017;3(12):1647–53.
11. Neff RT, Senter L, Salani R. Mutation in ovarian cancer: testing, implications and treatment considerations. Ther Adv Med Oncol. 2017;9(8):519–31.
12. Berek SJ, Hacker FN. Gynecologic oncology. 6th ed. Philadelphia: Wolters Kluwer; 2015.
13. UpToDate. Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: epidemiology and risk factors. Waltham, MA: UpToDate; 2018. Accessed 29 Mar 2019
14. Permuth-Wey J, Sellers TA. Epidemiology of ovarian cancer. Methods Mol Biol. 2009;472:413–37.
15. Doufekas K, Olaitan A. Clinical epidemiology of epithelial ovarian cancer in the UK. Int J Womens Health. 2014;6:537–45.
16. Hunn J, Rodriguez GC. Ovarian cancer: etiology, risk factors, and epidemiology. Clin Obstet Gynecol. 2012;55(1):3–23.
17. Beral V, et al. Ovarian cancer and oral contraceptives: collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. Lancet. 2008;371(9609):303–14.
18. Beral V, et al. Menopausal hormone use and ovarian cancer risk: individual participant meta-analysis of 52 epidemiological studies. Lancet. 2015;385(9980):1835–42.
19. Penninkilampi R, Eslick GD. Perineal talc use and ovarian cancer: a systematic review and meta-analysis. Epidemiology. 2018;29(1):41–9.
20. Beral V, et al. Ovarian cancer and smoking: individual participant meta-analysis including 28,114 women with ovarian cancer from 51 epidemiological studies. Lancet Oncol. 2012;13(9):946–56.
21. Prat J, F.C.o.G. Oncology, FIGO's staging classification for cancer of the ovary, fallopian tube, and peritoneum: abridged republication. J Gynecol Oncol. 2015;26(2):87–9.
22. Matz M, et al. Erratum to "Worldwide comparison of ovarian cancer survival: histological group and stage at diagnosis (CONCORD-2)" [Gynecol. Oncol. 144 (2017) 396–404]. Gynecol Oncol. 2017;147(3):725.

2 Ovarian Cancer Screening and Early Detection

Monica Levine and R. Wendel Naumann

Background

Approximately 1.3% of women born today, or 1 in 78, will be diagnosed with ovarian cancer at some point in their lifetime. This year there will be over 21,000 new cases of ovarian cancer along with nearly 14,000 deaths in the United States [1]. These cases arise from a much larger group of women presenting with pelvic masses. The overall prevalence of pelvic masses is estimated at 7% [2]. In addition, it is expected that 5–10% of American women will receive prophylactic surgery for suspected ovarian cancer at some point in their lives.

Ovarian cancer remains the leading cause of death from gynecological malignancy in the United States. A critical factor associated with the high incidence to mortality ratio is the late stage at diagnosis, largely due to the lack of early disease-specific symptoms or an effective strategy for early detection. The outcome for early-stage ovarian cancer is excellent with an 89% 5-year survival for patients with stage I cancer and 71% for stage II [3]. However, patients with ovarian cancer often do not have symptoms until the later stages of the disease and 63% of patients with epithelial ovarian cancer have already established regional or distant metastases at the time of diagnosis. Despite aggressive cytoreductive surgery and platinum-based chemotherapy, the 5-year disease-specific survival is 41% for stage III ovarian cancer and only 20% for stage IV ovarian cancer.

Carcinoma of the Müllerian epithelium includes cancer arising from the ovary, the fallopian tube, and the peritoneum. The site of origin of these tumors does not change clinical care and these cancers are often referred to collectively as "ovarian cancer." The origins of these cancers are now better understood and have implications for different screening strategies. There is a dual mechanism proposed for the origin of serous ovarian cancer with these cancers being divided into low-grade and high-grade subtypes with distinctly different developmental pathways [4]. The low-grade cancers are often confined to the ovary and develop through mutation in the PI3K growth pathway. These lesions likely start with a benign process and develop mutations that lead to borderline, micropapillary lesions, and low-grade cancers over a period of time. Low-grade cancers are much more likely to be detected early by screening and constitute a minority of deaths from ovarian cancer. It is now thought that most high-grade serous cancers start in the fallopian

M. Levine, MD
The James Cancer Hospital and Solove Research Institute, The Ohio State University College of Medicine, Columbus, OH, USA
e-mail: monica.levine@osumc.edu

R. W. Naumann, MD (✉)
Levine Cancer Institute, Atrium Health, Charlotte, NC, USA
e-mail: wendel.naumann@atriumhealth.org

© Springer Nature Switzerland AG 2022
S. A. Farghaly (ed.), *Advances in Diagnosis and Management of Ovarian Cancer*,
https://doi.org/10.1007/978-3-031-09169-8_2

tube [5]. Serous tubal intra-epithelial carcinoma (STIC) is a putative precursor of high-grade serous carcinomas. STIC lesions are described with P53 alterations and may spread throughout the peritoneal cavity prior to any detectable abnormality on imaging or even elevation of biochemical markers. This has likely been the reason that an effective screen strategy has been elusive in ovarian cancer. Most clear cell and endometrioid ovarian cancers are thought to arise from endometriosis, which can be ovarian or extra-ovarian [6–8]. Screening by imaging would likely only be able to detect ovarian cancers that developed in the ovary, which constitute a minority of cases. Primary ovarian mucinous neoplasms are rare and probably arise within benign mucinous tumors, which are also potentially detectable by screening ultrasound [9]. These revelations concerning the origins of ovarian cancer would explain why screening has had limited success in reducing the mortality from ovarian cancer. This also highlights the need for different approaches to ovarian cancer screening that will include the detection of the STIC lesions prior to spread throughout the peritoneal cavity.

Development of a Screening Test

Considering the low prevalence of ovarian cancer, any proposed screening strategy must demonstrate a reasonable sensitivity with a very high specificity to achieve a reasonable safety margin. Even at a specificity (SP) of 99.6% and a sensitivity (SN) of >75%, the positive value (PPV) of an ovarian screening test would only be 10% in an average-risk population. This is problematic because a positive screening test often leads to surgical intervention, so a screening test that yields a positive predictive value of less than 10% is not acceptable [10, 11].

The World Health Organization (WHO) has specified prerequisite criteria that must be met for a screening test to be effective [12]. Notably, a sufficient interval must exist between onset of early-stage disease and development of advanced disease to allow for screening and intervention. Although ovarian cancer satisfies many of the WHO requirements, several particular aspects of the etiology and epidemiology of ovarian cancer complicate the question of screening:

1. There is likely not a transition from stage I through stage III as the cancer disseminates from the fallopian tube into the peritoneal cavity before imaging can determine an abnormality.
2. Clinical evidence indicates that methods in common use today are not able to identify cancers early enough to significantly alter the natural history of the disease.
3. Approximately 90% of ovarian cancers occur in a low-risk population and the relative incidence is very low.
4. Given a low prevalence of ovarian cancer (40 per 100,000 per year) among postmenopausal women, screening tests must achieve a very high specificity rate to lower the positive predictive rate to acceptable levels.

Ovarian Cancer Symptom Index

A case control study has reviewed the symptoms present prior to detecting ovarian cancer [13]. In the evaluation of 149 women with ovarian cancer compared to 255 without, the following symptoms were included in an index of six symptoms: pelvic pain, abdominal pain, increased abdominal size, bloating, difficulty eating/feeling full, that when present >12 times a month for <12 months are significantly correlated with the diagnosis of ovarian cancer. For women ≥50 years, the sensitivity was 66.7% and the specificity was 90%. Subsequent studies evaluated the performance of the Ovarian Cancer Symptom Index (OCSI) in combination with biomarkers. A prospective case-control study of 74 women with ovarian cancer and 137 healthy women found that CA-125, HE4 and OCSI were independently predicted the presence of ovarian cancer. With a tool that requires two of the three tests to be positive, sensitivity was 83.8% overall, 67.7% for early-stage and 100% for high-risk cases. However, the specificity was 98.5%, which generated a positive predictive value below the threshold of 10% [14].

In a study to evaluate the potential harms of implementing the OCSI, 5012 women were prospectively evaluated using the OCSI and were offered CA-125 and TVUS if screened positive. A total of 241 women were positive on the screen with 211 having follow-up testing (CA-125, ultrasound or both) and 20 underwent surgery. Only 6 of those 20 surgeries were performed for a pelvic mass. Two women were diagnosed with ovarian cancer within 6 months of completing the OCSI. One of those women screened positive with the OCSI and was diagnosed at an advanced stage. The other was screen negative and was diagnosed at an early stage. There were an additional six cancers diagnosed after the initial 6 months follow-up period, three of which were diagnosed at an early stage. The authors were unable to make conclusions about the efficacy of the OCSI due to the small number of ovarian cancer diagnoses. However they did suggest that the OCSI may have played a role in educating women about the symptoms related to ovarian cancer—perhaps explaining the later diagnoses [14].

Biomarkers

A number of cell-surface antigens and serum proteins are produced by ovarian tumors and can be assayed using monoclonal antibodies. Some of these assays have been applied clinically as markers of disease status and may be useful in the detection of subclinical disease. However, the current indications for the uses of biomarkers are for the pre-surgical prediction of malignancy when a pelvic mass has been found and also to determine treatment response [15–18]. CA-125 is the most robust and well-known serum biomarker for detection of ovarian cancer. The initial finding of CA-125 levels greater than 35 U/mL in approximately 83% of patients with advanced epithelial ovarian cancer and in only 1–2% of the normal population led to investigations into its use as a biomarker for ovarian cancer [19, 20]. CA-125 levels vary significantly between pre- and postmenopausal populations. In a prospective analysis of women at high risk of developing ovarian cancer, the 98th percentile was found to be 35 U/mL in postmenopausal women and 50th percentile in premenopausal women [21]. Other analyses of CA-125 have revealed a number of limitations for the test. Although CA-125 is frequently elevated in advanced-stage ovarian cancer, the protein is elevated in less than 50% of stage I disease and is often normal in early-stage cancers and mucinous carcinomas [22–28]. Moreover, a number of benign and malignant conditions may result in falsely elevated CA-125 values [29, 30]. Additional factors may influence the CA-125 level, such as race/ethnicity, age, hysterectomy, smoking history, and obesity [31]. Despite these well-recognized limitations, CA-125 remains the most widely studied serum biomarker for ovarian cancer. The best currently available protocol for early detection of ovarian cancer, a combination of screening for elevated CA-125 and transvaginal ultrasound in the presence of elevated CA-125, does not meet the stringent criteria for cost-effectiveness espoused by the US Preventive Services Task Force [32–34]. As a result, no professional group currently recommends screening for ovarian cancer in the general population [29–31].

Other potential biomarkers have been identified in patients with ovarian cancer. These include the following: CA 15-3, CA 54/61, CA 19-9, TAG-72, OVX1, M-CSF, carcinoembriogenic antigen (CEA), cancer-associated serum antigen (CASA), lipid-associated sialic acid (LASA), urinary gonadotropin fragment (UGF), HER2/neu (ErbB2), EGFR, sICAM-1, VEGF, and lysophosphatidic acid [27, 35–43]. In addition, several members of the kallikrein family of proteins have been identified as potential serum markers of ovarian cancer [44–50]. The use of gene expression array analysis has identified a number of novel markers, including Human Epididymis Protein 4 (HE4), prostasin, and osteopontin [51–53]. Different combinations of these biomarkers have been tested with respect to sensitivity and specificity of the diagnosis of ovarian cancer as noted in Table 2.1. However, the sensitivity and specificity combinations are too low to be used in screening of an average-risk population.

Table 2.1 Multi-marker panels which discriminate benign from malignant pelvic masses

Panel	Cases	Controls	SN	SP	Reference
CA-125, β2-microglobulin, transthyretin, transferrin	144	509	95	81	Hogdall et al. [54]
CA-125, midkine, anterior gradient 2 protein	46	61	95	98	Rice et al. [55]
CA-125, G-CSF, IL-6, EGF, VEGF	44	37	87	93	Gorelik et al. [56]
CA-125, IL-7	187	45	69	100	Lambeck et al. [57]
CA-125, HE4, IL-2Rα, α1-antitrypsin, CRP, YKL-40, cellular fibronectin, CA 72-4, prostasin	149	350	90	89.9	Yip et al. [58]

SN sensitivity, *SP* specificity

Table 2.2 Multi-marker panels for the preoperative prediction of malignancy in a pelvic mass

Panel	Cases	Controls	SN	SP	Reference
ROMA (CA-125, HE4, menopausal status)	89	383	94	75	Moore et al. [64]
OVA1 (CA-125, transthyretin, β2-microglobulin, ApoA1, transferrin)	151	373	93	43	Ueland et al. [65]
OVA1 (CA-125, transthyretin, β2-microglobulin, ApoA1, transferrin)	92	402	92	54	Bristow et al. [17]
OVERA (HE4, FSH, CA-125, transferring, ApoA1)	92	402	95	69	Coleman et al. [18]
CA-125, HE4, IL-2Rα, α1-antitrypsin, CRP, YKL-40, cellular fibronectin, CA 72-4, prostasin	149	350	90	90	Yip et al. [58]

SN sensitivity, *SP* specificity

HE4 is a secreted glycoprotein product of the *WFDC2* gene which has shown great promise as a diagnostic biomarker for ovarian cancer and has also recently been approved by the US Food and Drug Administration for disease monitoring [59, 60]. Studies focusing on the potential use of HE4 as a biomarker of ovarian cancer suggest that it is elevated in over 50% of ovarian cancer patients whose tumors do not express CA-125 [61]. HE4 has also demonstrated greater sensitivity than CA-125 among early-stage ovarian cancer patients and greater specificity in comparison with benign ovarian lesions [61, 62]. A diagnostic assay for HE4 has been developed and commercialized by Fujirebio Diagnostics, Inc. (Malvern, PA), and the use of HE4 for ovarian cancer monitoring has been approved by the US Food and Drug Administration (FDA) [63]. Investigations into the use of HE4 as an ovarian cancer biomarker have proceeded both in the area of population-based screening and in the differential diagnosis of a pelvic mass. Despite a number of promising reports, it has become apparent that HE4 is not sufficiently sensitive or specific to function effectively as a stand-alone test. However, the combined use of CA-125 and HE4 in the differential diagnosis of pelvic masses has received a considerable amount of attention with respect to the sensitivity and specificity of detecting a malignant mass (Table 2.2), but the specificity for this combination is too low to be an effective screening tool in a low-risk population. With the exception of HE4, the identification of additional biomarkers associated with ovarian cancer has not translated into widespread clinical implementation.

It remains unlikely that any stand-alone biomarker-based screening test will be capable of

overcoming the 10% positive predictive level required for population screening. However, work has persisted based on the notion that biomarker testing may prove effective in sufficiently defined high-risk groups or as part of a multimodal screening strategy involving transvaginal ultrasound or an equivalent imaging method as a second-line test.

Ultrasound

Ultrasound is attractive as a screening tool given the relatively low cost and lack of ionizing radiation. Imaging of the ovary has been proposed as a strategy to detect changes in size and architecture that might precede the development of symptoms and detection by pelvic examination. The American College of Obstetrics and Gynecology (ACOG) recommends transvaginal ultrasound for evaluation of a suspected or an incidentally identified pelvic mass. A cyst greater than 10 cm in size, a mass with irregularities, papillary or solid components, high color Doppler flow, or the presence of ascites should raise concern for malignancy [66]. Ultrasound alone has been explored as a screening tool. The University of Kentucky Ultrasound Study screened women for epithelial ovarian cancers, including tumors with low-grade malignant potential, in a single-arm trial with annual ultrasound. This trial enrolled 25,327 women and the results showed an improved 5-year survival when compared to historical controls at the same institution (75% vs. 54%) [67]. However, a single-arm trial is difficult to interpret as patients participating in trials may not be typical of the general population. This effect was noted in the Prostate, Lung, Colorectal and Ovarian (PLCO) trial where the all-cause mortality was significantly reduced when compared to the general population [63].

The United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) enrolled 202,638 postmenopausal women between the ages of 50 and 74 years who were deemed to be at average risk for ovarian cancer. The ultrasound arm of the UKCTOCS trial screened 50,623 women with an annual ultrasound compared to 101,299 controls [68]. Ultrasound was repeated in 1 year if normal, 3 months if inconclusive, or 6 weeks if abnormal. Anyone with persistent abnormalities was evaluated by an National Health Service clinician. There was no difference in the number of early ovarian cancers or mortality between these two arms. Given the size of this trial it is unlikely that ultrasound alone will be able to significantly alter mortality in ovarian cancer.

The International Ovarian Tumour Analysis Phase 5 (IOTA-5) study prospectively followed women who were found to have adnexal masses considered to be benign by ultrasound to estimate the incidence of complications, including torsion, malignancy, or cyst rupture. An interim analysis of 3144 women 2 years after initial ultrasound found spontaneous resolution for 20.2%, and the incidence for complications low: 0.4% for invasive malignancy, 0.3% for borderline tumors, 0.4% for torsion, and 0.2% for cyst rupture. This study provides promising evidence that current algorithms to stratify risk of pelvic masses by ultrasound are a safe method of management of pelvic masses [69].

Multimodal

Biomarker testing is attractive due to the low cost and ease of testing. This type of screening can be combined with ultrasound or can be used to triage patients to ultrasound when abnormal to facilitate mass population screening. Three large, randomized trials designed to determine whether this multimodal ovarian cancer screening improves survival have reported their findings. In the PLCO Trial, 68,557 healthy postmenopausal women between the ages of 55 and 74 years were randomly assigned to undergo either annual CA-125 testing plus transvaginal ultrasound or to receive "usual care" [70]. A positive finding was defined as a CA-125 level of more than 35 U/mL or ultrasound evidence of an abnormal ovarian volume or an ovarian cyst with papillary projections or solid components. Diagnostic follow-up of positive screens was performed at the discretion of participants' physicians. The positive predictive value of a positive screening test was 1.0–1.3% during the 4 years of screening. The

overall ratio of surgeries to screen-detected cancers was 19.5:1. While screening did detect ovarian cancers, 72% of screen-detected cases were stage III or IV, suggesting that screening has not resulted in a significant stage shift [70]. The PLCO project team released its final report on survival in which they conclude that the CA-125/ultrasound screening approach does not reduce disease-specific mortality in comparison to usual care, but does result in an increase in invasive medical procedures and associated harms [71].

In Japan, the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) randomized 82,487 women to screening with ultrasound and CA-125 or to the control care with usual care (no screening) [72]. There was no significant difference in the detection of ovarian cancer. The mean follow-up in the trial was 9.2 years. A shift toward stage I cancers was seen in the study (63% versus 38%), but due to the relatively small numbers of cancers, this did not meet statistical significance.

In clinical trials, CA-125 as a single screening biomarker demonstrated limited utility when examined in a retrospective analysis of serum samples from 5550 women enrolled in a population-based registry in Sweden [73]. Later it was suggested that measurement of CA-125 values in an individual patient over time could improve the estimation of a patient's risk of ovarian cancer (Risk of Ovarian Cancer Algorithm (ROCA)) [74]. To evaluate CA-125 dynamics, the ROCA was developed based on the slope of serial CA-125 measurements drawn at regular intervals [75]. This algorithm was based on the observation that irrespective of the initial level, CA-125 measurements are stable in non-cases for periods of more than 5 years, indicating that each woman has her own baseline level of CA-125. In contrast, exponentially increasing serial values readily identify cases. When the ROCA score exceeds a 1% risk of having ovarian cancer, patients undergo TVU to determine whether additional intervention is warranted. In a retrospective examination of 33,621 serum samples from 9233 women, ROCA provided a sensitivity of 86% at a fixed specificity of 98% for the preclinical detection of ovarian cancer, compared to a sensitivity of 62% for a single CA-125 value [75]. This algorithm was confirmed to have a reasonably high positive predictive value (19%) in a subsequent prospective pilot study involving more than 13,000 postmenopausal women [76]. This ROCA algorithm was tested in a population-based screening effort in the UKCTOCS trial. This trial enrolled 202,638 postmenopausal women between the ages of 50 and 74 years who were deemed to be at average risk for ovarian cancer. Women in the UKCTOCS trial were randomly assigned to undergo annual pelvic examination (control group), annual transvaginal ultrasound (ultrasonography or USS group), or annual measurement of CA-125 evaluated over time with the use of ROCA plus transvaginal ultrasound in cases in which the ROCA was abnormal (multimodality screen or MMS group) [75, 77]. Women with persistent abnormality on repeat screens underwent evaluation by a clinical oncologist and, where appropriate, surgery. As compared with ultrasonography alone, multimodality screening had a significantly greater specificity (99.8% vs. 98.2%) and a higher positive predictive value (35.1% vs. 2.8%) ($P < 0.001$). The trial was negative with respect to the primary endpoint of reducing ovarian cancer mortality, but 25% of women in the MMS group were diagnosed at stage I as compared to 16% in the control group. While this shift toward an earlier stage is encouraging, it is predicted that this shift would likely only reduce ovarian cancer mortality by a modest 6–9% and is cost prohibitive [78]. Because of the relative lack of effectiveness and the possibility that screening could give false reassurance, the FDA ruled against using this test in the United States [79]. This strategy is currently being prospectively studied among more than 2600 high-risk women by the Gynecologic Oncology Group (protocol #199) as well as in a parallel trial being conducted by the National Cancer Institute-Cancer Genetics Network [80].

Current Screening

There have been several screening trials that have evaluated the use of ultrasound with CA-125 measurements in the general population. Combining biomarkers CA-125 or HE-4 with the Ovarian Cancer Symptom Index (OCSI) is