Screening and Prevention of Ovarian Cancer

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Abstract

The aim of this study is to review clinical studies for organizing a screening and prevention program for ovarian cancer. A search of the relevant English-language literature published between 1986 and 2016 was conducted using the MEDLINE online database. Several reviews have dealt with ovarian cancer screening in the general populations and specific high-risk groups. The results from the medical literature showed that a variety of screening of ovarian cancer were unable to provide the impact on clinical survival benefit. Although the survival data from the UK study provided a modest degree of hope, at present there is no effective screening test for ovarian cancer. Since ovarian cancer is not a uniform entity, it is unlikely that a single approach to screening will be appropriate for all patients. Clinical guidelines are available for HBOC, which include breast and ovarian cancer screening (surveillance) and risk-reducing interventions (risk-reducing surgical and medical options). Surgical and pharmacological options are available. Prophylactic RRSO and RRM reduced cancer incidence compared to chemoprevention or surveillance, but many women who are at risk for BRCA1/2 mutations delay or decline prophylactic surgery. Oral contraceptives are proposed as a chemoprevention agent for ovarian cancer. Chemoprevention contributes to reducing ovarian cancer deaths, with a special attention on the breast cancer risk. Importantly, a recent meta-analysis demonstrated a significant ovarian cancer risk reduction and no increased breast cancer risk with oral contraceptive use by BRCA mutation carriers. Breast cancer risk may vary by age at first oral contraceptive use, duration of use, intervals

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H. Katabuchi (ed.), *Frontiers in Ovarian Cancer Science*, Comprehensive Gynecology and Obstetrics, DOI 10.1007/978-981-10-4160-0_4

from the last use, and oral contraceptive formulation. At present, there is no effective screening for ovarian cancer. Clinicians are recommended to encourage high-risk women who delay or decline risk-reducing surgery to discuss risk-reducing pharmacologic options in order to prevent ovarian cancer progression without elevation of breast cancer risk.

Keywords
Screening • Prevention • Ovarian cancer • Breast cancer

4.1 Introduction

Epithelial ovarian cancer (EOC) is the leading cause of cancer death among all gynecological malignancies worldwide. More than 50% of patients have already reached to the advanced stages of disease in which 5-year survival rate is <40%. The incidence of sporadic and hereditary EOC increases with age. EOC, highly heterogeneous histological appearances, including serous, clear cell, endometrioid, and mucinous carcinomas, was divided into type I and type II tumors [1]. At least the type I tumors are mostly low-grade, low-growing, and well- or intermediately differentiated tumors of endometrioid or clear cell histological subtype. They demonstrate a stepwise progression from a benign precursor such as endometriosis to atypical endometriosis as an intermediate lesion and subsequently to endometriosis-associated ovarian cancer (EAOC). EAOC was frequently diagnosed at a younger age and an earlier stage of disease with favorable clinical outcome compared to high-grade serous carcinoma. A number of specific genetic alterations, like loss of heterozygosity (LOH), microsatellite instability, PTEN (phosphatase and tensin homolog), KRAS (KRAS proto-oncogene, GTPase), CTNNB1 (catenin beta 1), and ARID1A (AT-rich interaction domain 1A) mutations, have been found in EAOC. In contrast, type II tumors, including high-grade serous carcinoma (HGSC), are clinically aggressive, accompanied by rapid growth and present in advanced stage with unfavorable clinical outcome. Among EOC, HGSC accounts for 70–80% of cancer deaths. Deleterious point mutations in tumor suppressor genes, such as TP53 (tumor protein p53), BRCA1 (BRCA1, DNA repair associated), and BRCA2, are relatively common in HGSC. Mutations of BRCA1 and BRCA2, the most frequently affected genes, are associated with the hereditary breast and ovarian cancer (HBOC) syndrome. BRCA1/2 mutation carriers have an increased risk of developing breast cancer and gynecologic cancers including ovarian, fallopian, and peritoneal cancers. This type of ovarian cancers might originate from the distal end of the fallopian tube (fimbria), but not from the precursor cells in the ovarian surface epithelium as previously believed [2]. Morphologically transformed cells with p53 mutations cannot be detected in inclusion cysts of the ovary in a series of prophylactic oophorectomy specimens [3]. Widespread disease can be diagnosed <6 months after a negative surveillance using transvaginal sonography (TVS) and CA125 test [4].

Epidemiologic studies have identified that nulliparity, age at first pregnancy, early menarche, late menopause, a greater number of ovulatory cycles, cumulatively summed as lifetime number of ovulatory cycles, infertility, obesity, and hormone replacement therapy have been associated with definite risks of ovarian cancer. Protective factors have been identified, which include oral contraceptive use, multiparity, hysterectomy, tubal ligation, breastfeeding, prior oophorectomy, and NSAID and oral contraceptive use [5].

Interestingly, there is a significant difference by race in the histology of EOC [6]. Of Caucasians, 70–80% had HGSC and <10% had clear cell carcinoma. Of Asians (or Japanese), 40% had HGSC and 25% had clear cell lesions. Type II tumors are significantly common in Caucasians, and the rate of type I tumors is relatively higher in Japanese than in Caucasians. Japanese researchers have been trying to identify suitable or novel screening methods that enable stratification of patients with type I ovarian cancer for optimal screening (see Sect. 4.4.4).

Population-based cancer screening programs for breast, lung, gastric, colon, and cervical cancers allow an early diagnosis, even before the onset of symptoms. Effective screening methods have impacted on a cost-effective prevention and survival in these cancers. Ovarian cancer screening strategies are as follows: to identify women without symptoms in an early stage allowing curative treatment; to improve survival for the screeners versus non-screeners; to avoid false-positive findings, leading to unnecessary workup or surgery; to avoid causing harm to the women who do not have the disease; and routine screening or surveillance for early detection is not costly. An effective screening requires a sufficient time interval from initiation to the metastatic stage, namely, a sufficient window for early detection. Indeed, ovarian cancer cells rapidly spread in the peritoneum, and most diseases are diagnosed at an advanced stage. The endeavor may be hindered because of the lack of cost-effective screening strategies.

Several reviews have dealt with ovarian cancer screening in the general populations and specific high-risk groups. The ideal strategy for surveillance of high-risk ovarian cancer has become increasingly challenging. The purpose of this article is to critically review the published literature on the factors associated with ovarian cancer screening and prevention program. Since EOC is not a uniform entity, it is unlikely that a single approach to screening will be appropriate for all patients. The goal is to identify modifiable screening methods for the Japanese population.

4.2 Materials and Methods

4.2.1 Search Strategy and Selection Criteria

A literature review was conducted to identify screening and prevention program for ovarian cancer. MEDLINE search via PubMed, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) of the relevant literature

published between January 1, 1986, and July 31, 2016, was systematically performed using the following keywords: “epithelial ovarian cancer,” “breast cancer,” “screening,” “prevention,” “general population,” “high-risk population,” “HBOC,” “BRCA1,” and “BRCA2.” English-language publication search results from MEDLINE and references within the relevant articles were analyzed. Furthermore, references within the references were searched to identify additional relevant studies.

4.3 Results

4.3.1 The Systematic Literature Review

The systematic search resulted in the identification of 1617 citations, and 56 additional studies were identified through manual searches of accepted studies and published systematic reviews. Of the 1673 citations identified in the search, 1286 were further excluded following abstract screening. Of the 387 full-text articles retrieved and reviewed, we selected RCTs and prospective studies. Overall, 35 studies (17 for ovarian cancer screening and 18 for ovarian cancer prevention) were included in this review.

4.3.2 Ovarian Cancer Screening in the General Population

In the general populations, it is prudent to target an older population, especially postmenopausal women. The serum marker CA125 and transvaginal sonography (TVS) have received the most attention to date.

4.3.2.1 CA125

CA125 is a high molecular weight transmembrane mucin (MUC16). This marker, currently the most widely used tumor marker for EOC, was elevated in serum from 90% of patients with advanced EOC and released into blood from cancer cells, possibly through the tumor necrosis factor (TNF)-alpha and interferon (IFN)-gamma stimulation [7]. CA125 was originally developed to monitor patients previously diagnosed with ovarian cancer. To date, CA125 can help in the evaluation of an adnexal mass in appropriate patients. In most studies, CA125 was elevated in approximately 50–60% of stage I disease, demonstrating that this marker is not sufficiently sensitive to detect all cases of early-stage ovarian cancer [8]. In addition, a number of common benign conditions, including endometriosis, adenomyosis, ovarian cysts, uterine fibroids, renal dysfunction, hepatic disease, and inflammation, can cause elevation of CA125 levels. In ovarian cancer patients, an exponential rise is seen in CA125 level before clinical detection of diseases, which was documented in some studies [9]. Taken together, CA125 alone was not recommended as a screening test in asymptomatic women, because of its low sensitivity and limited specificity.

Table 4.1 A summary of the key findings of the two ovarian cancer screening trials using CA125

	St Bartholomew's Hospital trial	The Boston study
Ref.	[9]	[10]
Published	1996	2003
Design	Single arm prospective study	Single arm prospective study.
Subjects	The low-risk asymptomatic women > or = 45 years of age. 22,000 volunteers	33,621 CA125 results from 9233 low-risk women older than 45 years for whom two or more serial samples were available
Recruitment	Between June 1, 1986 and May 1, 1990, London	Between June 1, 1986, and May 1, 1990
Strategy	CA125 measured annually for 1–4 years and a positive CA125 was recalled for ultrasound	CA125 II levels
Interpretation	A CA125 concentration > or = 30 U/mL	Calculation based on serial CA125 II levels
Results	The relative risk of developing ovarian and fallopian cancers within 5 years was increased 14.3-fold (8.5–24.3) after a CA125 cut-off > or = 30 U/mL and 74.5-fold (31.1–178.3) after a cut-off > or = 100 U/mL	The risk calculation significantly improved the area under the curve from 84 to 93% compared with a fixed cutoff for CA125. CA125 achieved a sensitivity of 62%
Mortality	Serial CA125 elevation is associated with an increase in risk of an index cancer in asymptomatic women older than 45 years. The mortality effect has not been reported as yet	Serial CA125 elevation improved the ovarian cancer detection rate in asymptomatic women. The mortality effect has not been reported as yet

Although an effective strategy must meet the stringent requirement of screening, several studies have reported ovarian cancer screening trials that have been conducted using CA125 in postmenopausal women in the general population. Table 4.1 is a summary of the key findings of the two ovarian cancer screening trials using CA125. In the Boston study, serial CA125 elevation contributed more significantly to successfully predict the risk of ovarian cancer compared with a fixed cutoff in asymptomatic women older than 45 years [10]. However, the survival benefit has not been reported as yet. At present, CA125 alone cannot be recommended for screening for ovarian cancer in asymptomatic women [11]. Given the heterogeneity of EOC, a panel of biomarkers may be more effective than a single marker. CA125 is more often negative in clear cell carcinoma than in other subtypes of EOC. Recent study has demonstrated that a new marker TFPI2 may be useful for detection of clear cell carcinoma [12]. Current biomarkers including TFPI2 will be investigated in combination with CA125 in larger cohorts to improve ovarian cancer diagnosis.

4.3.2.2 Transvaginal Sonography

Transvaginal sonography (TVS) has been considered a primary imaging modality for diagnosing and evaluating adnexal masses. TVS has high specificity and sensitivity for detecting an adnexal mass based on a pattern recognition approach and

morphological feature through gray-scale ultrasound. Table 4.2 is a summary of the findings of the four major ovarian cancer screening trials using TVS. These studies used gray-scale TVS as a primary screening modality [13, 14, 16, 17]. The percentage of the total number of stage I cases increased after the induction of screening (stage shift). It was not effective in detecting ovarian cancers in women who had normal ovarian volume. The use and role of Doppler ultrasonography as a screening technique are controversial. Color flow imaging for detection of ovarian cancer greatly improves specificity but at the expense of potential sensitivity in the triage of adnexal masses. Dr. van Nagell and his colleagues have reported some encouraging evidence of not only stage shift but also survival benefit by a single-arm prospective study, not a RCT [18]. A large-scale RCT is required for answering this question. Further, stringent quality control and quality assurance are necessary for TVS screening of asymptomatic postmenopausal women.

4.3.2.3 Two-Stage Strategies

Several studies have assessed the diagnostic value of combinations of CA125 and imaging concurrently or sequentially to augment the specificity and sensitivity for screening. Clinicians and public health informants were in consensus that the key issue is to reduce mortality. Table 4.3 is a summary of the key conclusions from the five major ovarian cancer screening trials using CA125 and TVS.

First, Jacobs and coworkers studied a group of 1010 asymptomatic postmenopausal women, comparing the specificities of individual evaluation or a combination of CA125, TVS, and pelvic examination (the first London study) [19]. Their study showed a specificity of 99.8% and 99.0% for CA125 plus TVS and CA125 plus pelvic examination, respectively, indicating that the combination of CA125 with TVS achieved acceptable specificity.

In the second study (a pilot randomized controlled trial in the second London study) conducted in the UK by Jacobs and coworkers, the specificity of CA125 alone or in combination with abdominal ultrasound was evaluated in postmenopausal women 45 years of age or above [20]. The subjects were divided into a control group (10,977) and a screened group (10,985). A total of 16 and 21 cancers were detected in the screened and control group, respectively, during the same interval. Median survival in the screened group (72.9 months) was significantly greater than in the control group (41.8 months) [20].

Third, the original intention in the Shizuoka study (RCT with one screening strategy in study group) conducted in Japan by Kobayashi and coworkers was to offer women in the intervention group annual screens by gynecological examination (sequential TVS and serum CA125 test) [21]. Women with abnormal TVS findings and/or elevated CA125 values were referred for surgical investigation by a gynecological oncologist. Twenty-seven index cancers were detected in the 41,688 screened women. Eight cancers were diagnosed outside the screening program. Among the 40,779 control women, 32 women developed ovarian cancer. The detection rate of early-stage ovarian cancer was elevated in the screened group compared with the controls, which did not reach statistical significance (63% vs 38%, $p = 0.2285$). Interestingly, sub-analysis assessment identified that the Shizuoka screening

Table 4.2 A summary of the findings of the four major ovarian cancer screening trials using TVS

	The London study	The First Kentucky study	The Hirosaki, Japan study	The Second Kentucky study	The Third Kentucky study
Ref.	[13]	[14, 15]	[16]	[15, 17]	[15, 18]
Published	1993	2000	2000	2007	2011
Design	Single arm prospective study	Single arm prospective study	Single arm prospective study	Single arm prospective study	Single arm prospective study, not a RCT
Subjects	1601 self referred asymptomatic women aged 17 to 79 (mean 47) years, with a family history of ovarian cancer, aged 17 to 79 (mean 47) years. 60% were premenopausal	14,469 asymptomatic women; women >/= 50 years of age in the general populations and women >/= 25 years of age with a family history of ovarian cancer	51,550 low-risk asymptomatic women who participated in annual uterine cervical carcinoma screening.	25,327 asymptomatic women aged > or = 50 years in the general populations and women aged > or = 25 years who had a family history of ovarian cancer	37,293 asymptomatic women aged > or = 50 years in the general populations and women aged > or = 25 years who had a family history of ovarian cancer
Recruitment		Between 1987 and 1999	Between 1989 and 1999	Between 1987 and 2005	Between 1987 and 2011
Strategy	Transvaginal ultrasonography with color blood flow imaging	Annual transvaginal sonography (TVS)	Annual transvaginal sonography (TVS)	Annual transvaginal sonography (TVS)	Annual transvaginal sonography (TVS). Women with abnormal screens underwent tumor morphology indexing, serum biomarker analysis, and surgery
Interpretation	Morphological score > or = 5 and pulsatility index <1.0	An abnormal sonogram	An abnormal sonogram (a mass > 30 mm in greatest dimension or a mass with a mixed pattern)	An abnormal sonogram	An abnormal sonogram

(continued)

Table 4.2 (continued)

	The London study	The First Kentucky study	The Hirosaki, Japan study	The Second Kentucky study	The Third Kentucky study
Results	61 women had a positive screening result (3.8%, 95% confidence interval 2.9 to 4.9%), six of whom had primary ovarian cancer detected at surgery (five stage Ia, one stage III)	180 patients with persisting TVS abnormalities underwent exploratory laparoscopy or laparotomy. 17 ovarian cancers were detected: 11 Stage I, 3 Stage II, and 3 Stage III. Four and four patients developed ovarian cancer within 12 months of a negative scan and more than 12 months following a normal screen, respectively. Statistical variables: sensitivity, 81%; specificity, 98.9%; positive predictive value, 9.4%; and negative predictive value, 99.97%	Secondary screening was required for 5309 participants (10.3%). Surgery was performed on 324 participants. Twenty-two primary tumors and 2 metastatic tumors were detected for a diagnostic rate of 0.047%. 77.3% were classified as Stage I carcinoma.	Among 364 patients (1.4%) with a persisting ovarian tumor, 35 primary invasive ovarian cancers, 9 serous ovarian tumors of low malignant potential, and 7 cancers metastatic to the ovary were detected. Nine women developed ovarian cancer within 12 months of a negative screen. A sensitivity of 85.0%, specificity of 98.7%, positive predictive value of 14.0%, and negative predictive value of 99.9%	Forty-seven invasive epithelial ovarian cancers and 15 epithelial ovarian tumors of low malignant potential were detected. Stage distribution: stage I, 47%; stage II, 23%; stage III, 30%, and stage IV, 0%. The 5-year survival rate for all women with invasive index cancer detected by screening as well as interval cancers was 74.8% compared with 53.7% for unscreened women with ovarian cancer ($P < 0.001$)

Mortality	TVU with color flow imaging can effectively detect early ovarian cancer in women with a family history of the disease. The mortality effect has not been reported as yet	A decrease in stage at detection (stage shift) and a possible decrease in case-specific ovarian cancer mortality	Stage shift may decrease the mortality of the disease. The mortality effect in comparison with the non-screening group has not been reported as yet	Stage shift. Although a significantly higher fraction of early-stage cancer was detected, they also had nine patients who developed ovarian cancer within 12 months of a normal scan. The mortality effect in comparison with the non-screening group has not been reported as yet. Although a significantly higher fraction of early-stage cancer was detected, they also had nine patients who developed ovarian cancer within 12 months of a normal scan	Some encouraging evidence of stage shift and survival benefit

Table 4.3 A summary of the key conclusions from the five major ovarian cancer screening trials using CA125 and TVS

	The First London study	The Second London study	Japanese Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS)	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States of America (USA)	United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
Ref.	[19]	[20]	[15, 21]	[15, 22, 23]	[15, 24, 25]
Published	1988	1999	2008	2016	2016
Design	Single arm prospective study	A pilot randomized controlled trial	RCT with 1 screening strategy in study group	RCT with 1 screening strategy in study group	RCT with 2 screening strategies in study group
Subjects	1010 low-risk asymptomatic postmenopausal women	The low-risk postmenopausal women aged 45 years or older. Randomized to a screened group (n = 10,958) or control group (n = 10,977)	41,688 low-risk asymptomatic postmenopausal women. Either an intervention group (n = 41,688) or a control group (n = 40,799), with follow-up of mean 9.2 years	78,216 low risk asymptomatic women aged 55 to 74 of whom 39,105 underwent screening	An RCT of 202,638 low risk asymptomatic women aged 50–74 years from the general population randomized in 2001–2005 to no intervention (control: 101,359) or annual screening using either TVS alone (50,639) or serum CA125 interpreted by a 'Risk of Ovarian Cancer' algorithm (ROCA) with TVS as a second line test (multimodal screening, MMS; 50,640)

Recruitment	For an ovarian cancer screening programme	Between 1989 and 1998	Between 1985 and 1999	Between 1993 and 2007, at a median follow-up of 12.4 years (25th–75th centile 10.9–13.0)	Randomized in 2001–2005
Strategy	CA125 measurement and vaginal examination as initial tests and real-time ultrasonography as a secondary procedure in selected cases	Multimodal screening with sequential CA 125 and TVS to detect invasive epithelial cancers of the ovary or fallopian tube (index cancers). In the screened group, CA125 was measured annually for 3 years	Physical exam, ultrasound and CA125 concurrently	Ultrasound and CA125. The women were screened using serum CA125 and TVS for 4 years followed by CA125 alone for a further 2 years. The patients with pelvic lesions or an elevated CA125 level were referred to their local physicians for further management	Two screening arms (TVS) and CA125 followed by ultrasound (MMS)
Interpretation	The normal range for serum CA125 in postmenopausal women was established	CA 125 was 30 U/mL or more	CA125 using a 35 U/mL cutoff	CA125 using a 35 U/mL cutoff and/or an abnormal sonogram	CA125 interpreted using the Risk of Ovarian Cancer algorithm (ROCA). The ROCA is a statistical tool that considers current and past CA125 values to determine ovarian cancer risk

(continued)

Table 4.3 (continued)

	The First London study	The Second London study	Japanese Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS)	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial in the United States of America (USA)	United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)
Results	The combinations of serum CA125 measurement with ultrasound and vaginal examination with ultrasound achieved specificities of 99.8% and 99.0%, respectively. 100% specificity was achieved by serum CA125 measurement with vaginal examination and by the combination of all three tests	Of 468 women in the screened group with a raised CA125, 29 were referred for a gynecological opinion; screening detected an index cancer in six and 23 had false-positive screening results. The positive predictive value was 20.7%. Median survival of women with index cancers in the screened group was 72.9 months and in the control group was 41.8 months ($p = 0.0112$). The number of deaths from an index cancer did not differ significantly between the control and screened groups (18 of 10,977 vs. nine of 10,958, relative risk 2.0 [95% CI 0.78–5.13])	Encouraging sensitivity (77.1%) for primary ovarian cancer. Stage shift: more Stage I ovarian cancers in the screened group (63%) compared to the control (38%), which did not reach statistical significance. The Japanese screening trial enables diagnosis of EAOC at an early stage of the disease.	Lower sensitivity (69.5%); only 28% were Stage I/ II. Abnormal TVS and elevated CA125 were found in 4.7%, and 1.4% of the participants, respectively. The positive predictive value for detection of ovarian cancer for CA125 alone and for TVS alone was 3.7% was 1.0%, respectively. The PPV for both tests combined was 23.5%, but 60% of early-stage disease would have been missed [5]. 118 and 100 deaths were reported in the screening and control arm, respectively, with a mortality rate ratio of 1.18 (95%CI 0.91–1.54)	Encouraging sensitivity (89.4% MMS/84.9% TVS) for primary index cancer; 84.9% MMS/75.0% TVS for primary invasive index cancer (47% MMS/50% TVS were Stage I/II). Superior sensitivity (88.6% vs 65.8%) and PPV (21.7% vs 5.8%) of MMS compared to the TVS arm for detection of primary invasive index cancers during incidence screening, with 40.3% in the MMS and 51.5% in the TVS arm detected at early stage

Mortality	The combination of CA125 with ultrasound achieved acceptable specificity. The mortality effect has not been reported as yet	A larger randomized trial to see whether screening affects mortality	The mortality effect has not been reported as yet	No mortality benefit. Screening with concurrent CA 125 and TVS has no evidence of a mortality benefit	The stages at detection were relatively earlier (stage I/II: 44%) in the screening cohort. Although the mortality reduction was not significant in the primary analysis, researchers noted a significant mortality reduction with MMS when prevalent cases were excluded. MMS significantly reduced ovarian cancer mortality after excluding either deaths in the first 7 years after randomization or prevalent cancers. The large number of false positive surgeries (roughly 2100 surgeries) would be needed in order to prevent the small cancer deaths (about 40 deaths in each screening group)

favorably detected certain histotypes such as clear cell and endometrioid types that are more common, low-grade, and less aggressive tumors in Japan. Since the progression of endometriosis to cancer is usually slow, recognition of patients at early stages may improve survival.

Fourth, the prostate, lung, colon, and ovary (PLCO) screening trial in the USA aimed to conduct concurrent testing of CA125 and TVS in the low-risk asymptomatic women between 55 and 74 years of age to determine if screening could reduce mortality in these cancers [22]. This RCT of screening versus usual care was initiated in 1993 and has studied 78,216 women. Data from the PLCO trial has not shown mortality benefit [15, 22, 23].

Finally, the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) used the risk of ovarian cancer algorithm (ROCA) to interpret the impact of CA125, which has shown an encouraging sensitivity and specificity [15]. The mortality reduction was not significant in the primary analysis, but this trial may have the potential to make an impact on survival benefit when prevalent cases were excluded [24]. The survival data from the UKCTOCS study provide a modest degree of hope.

Given the paucity of randomized controlled trial data, at present there is no effective screening test for ovarian cancer. The previous RCT results are unable to provide the impact on clinical survival benefit. This allowed us to explore the impact of growing insights into disease etiology and biomarker discovery on future screening strategies. In an era of promising advances in ovarian cancer screening, researchers have to focus on detecting low-volume disease using cancer-specific markers and targeted imaging. More cost-effective approaches might utilize novel biomarkers alone or in combination with imaging modalities in a more limited number of women.

4.3.3 Ovarian Cancer Screening in the High-Risk Population

Hereditary breast and ovarian cancer (HBOC) syndrome accounts for 5%–10% of breast cancers and 15% of invasive ovarian cancers [26]. Mutations in two genes, BRCA1 and BRCA2, are associated with HBOC. The average lifetime risk of EOC in the general populations is 1.3%, but the risk is markedly increased in women who carry mutations of the BRCA1 or BRCA2 (40% and 18% risk, respectively, by age 70 years) or the mismatch repair genes of hereditary nonpolyposis colorectal cancer (Lynch) syndrome (12% lifetime risk) [27–29]. Women with BRCA mutations have a markedly increased risk of early-onset breast, ovarian, pancreatic, and other cancers when compared to the risks in the general population. EOC is a spectrum of several subtypes, with different clinicopathological characteristics, possibly separate pathways of progression, and different sets of genetic and epigenetic characteristic of familial versus sporadic tumors. Since the molecular biology of the known hereditary disease may differ from that of sporadic cancer, separate trials and screening strategies may be required to detect hereditary and sporadic ovarian cancer. The overall occult gynecological carcinoma has been detected in 9.1% of BRCA

mutation carriers [30]. Clinical guidelines are available for HBOC, such as those published by the National Comprehensive Cancer Network (NCCN), which include breast and ovarian cancer screening (surveillance) and risk-reducing interventions (risk-reducing surgical and medical options) [30, 31]. Published guidelines adopt standardized surveillance strategies that limit medication side effects, medical/surgical exposure without compromising cancer control and unnecessary cost, as well as enhance overall clinical and economic outcomes.

4.4 Prevention of Ovarian Cancer

Potential preventive strategies against breast and ovarian cancer are the mainstay of cancer risk management and for improving quality of life in BRCA mutation carriers. Surgical and pharmacological options are available.

4.4.1 Risk-Reducing Surgical Options

4.4.1.1 Risk-Reducing Salpingo-Oophorectomy (RRSO)

The prospective studies on the efficacy of RRSO in BRCA mutation carriers showed a significant reduction in the risk of breast and ovarian cancer-specific mortality (hazard ratio [HR] 0.44 and HR 0.21, respectively) [32]. The risk stratification data revealed that the risk of ovarian cancer is 10–21% by age 50 in BRCA1 mutation carriers, whereas BRCA2 mutation carriers have a 2–3% risk of ovarian cancer by age 50. Without any prophylactic therapeutic interventions, the likelihood ratio of survival to the age of 70 was 53% for BRCA1 and 71% for BRCA2 mutation carriers. The only effective and economical surgical strategy to control this disease was RRSO at age 40 plus RRM at age 25, which improves survival to 79% in BRCA1 and to 83% in BRCA2 mutation carriers. After RRSO at age 40, BRCA1 and BRCA2 mutation carriers had a 37% and 64% risk reduction for breast cancer, respectively. Delay in RRSO from age 40 to age 50 decreased the survival gain from 15 to 8% in BRCA1 mutation carriers and from 6 to 4% in BRCA2 mutation carriers. This analysis revealed that delaying RRSO until the early 40s for the BRCA2 mutation carrier appears safe [33] but does not provide breast cancer risk reduction [32]. Furthermore, delaying RRM until age 40 or replacing RRM with breast cancer screening decreased survival gain [32, 34]. In BRCA mutation carriers with a history of breast cancer, RRSO reduced breast cancers in the ipsilateral and contralateral breast, but other study showed that RRSO did not alter the risk of a second primary breast cancer [35, 36]. Taken together, the NCCN recommends RRSO between 35 and 40 years of age, upon completion of childbearing and based on the age of the youngest affected relative with an ovarian cancer diagnosis, regardless of the type of BRCA mutation [31]. Since changes in sexual function, body image, menopause quality of life, and psychological functions are common outcomes following RRSO, long-term follow-up will be needed and critical to a full understanding of the late medical impact of RRSO. Actually, many women do not undergo

prophylactic surgery because of stress and anxiety [37, 38]. Rates of the surgery vary depending on balance between anxiety reduction and complications of surgery.

4.4.1.2 Risk-Reducing Oophorectomy (RRO)

BRCA germline mutation carriers are not only at risk for ovarian and breast cancer but also for primary fallopian tube carcinoma and peritoneal carcinoma. Some articles have compared the efficacy of patients with prophylactic bilateral risk-reducing oophorectomy (RRO) in the risk of fallopian tube carcinoma and peritoneal carcinoma to those of RRSO [39–41]. RRO has been chosen by some women with BRCA1 or BRCA2 mutation carriers as an alternative for RRSO. RRO reduces the risk of coelomic epithelial cancer (HR, 0.04; 95 percent confidence interval, 0.01–0.16) and breast cancer (HR, 0.47; 95 percent confidence interval, 0.29–0.77) in women at high-risk ovarian cancer due to inherited predisposition. Among the women with BRCA1 or BRCA2 mutations who chose RRSO, peritoneal cancer was not diagnosed in this group [41]. In contrast, primary peritoneal carcinoma has developed in 1.9% [40], 10.7% [39], and 11.5% [41] of women after RRO. Taken together, RRO may be ineffective in preventing papillary serous peritoneal cancer.

4.4.1.3 Risk-Reducing Salpingectomy (RRS)

Risk-reducing salpingectomy (RRS) with ovarian retention has been proposed as a bridge to RRO, due to evidence that ovarian cancer precursor lesions (e.g., serous tubal intraepithelial carcinoma, STIC) in BRCA mutation carriers may originate in the distal fimbrial end of the fallopian tubes [42]. RRS has the net clinical benefit, including sparing the ovaries until future oophorectomy (longer maintenance of ovarian function), offering delay of surgical menopause (delaying negative effects of early surgical menopause) and allowing for preservation of some reproductive options [43]. RRS has been suggested as a risk-reducing strategy for BRCA1/2 mutation carriers [44], but delay in RRO theoretically could reduce the protective effect against breast cancer. Although RRS should be considered an investigational risk management option, the application of prophylactic surgeries may reduce the incidence of ovarian cancer (65% risk reduction by RRS and 96% by RRSO) [45]. Prophylactic RRSO may provide greater benefits with the view of reducing the risk for ovarian cancer compared to RRS.

It has been reported that majority of cases with ovarian HGSC arise in the fallopian tube fimbria [46]. Furthermore, in the BRCA1/2 mutation carriers, the microscopic cancers were confined to not only the fallopian tubes but also ovaries only or peritoneal washings only, suggesting that the site of origin may be in the fallopian tube, ovary, or peritoneum [47]. This suggests that cancer initiation may occur in the fallopian tube fimbriae, but tumor growth and progression are favored in the ovary. Quite a lot of information may exist in favor of a cancer progression role of ovarian surface epithelium or inclusion cyst. Ovulation-induced inflammation and oxidative stress may induce genotoxic damage leading to ovarian carcinogenesis. Currently, RRS is not included in the NCCN guidelines as strategies for risk reduction in BRCA mutation carriers. Additional evidence is needed regarding the effectiveness

of the surgical options such as RRS and RRO for cancer risk reduction. It remains unclear whether oral contraceptives would be useful in a decreased risk of ovarian cancer after RRS in BRCA mutation carriers.

4.4.1.4 Tubal Ligation

Tubal ligation has been associated with the risk reduction of ovarian cancer, particularly in the type II ovarian cancer, in the general populations [5]. There are a few small studies of ovarian cancer risk reduction with tubal ligation in BRCA mutation carriers. In a case-control study, a history of tubal ligation was associated with a decrease in risk for ovarian cancer in BRCA mutation carriers [48]. In contrast, tubal ligation may not be protective against ovarian cancer for BRCA mutation carriers [49]. It remained controversial that tubal ligation has the clinical benefit in the high-risk groups.

4.4.2 Risk-Reducing Pharmacologic Options

The NCCN guidelines recommend that BRCA mutation carriers could be followed with pelvic examinations, transvaginal ultrasounds, and serum CA125 levels every 6 months beginning at age 30 or 5–10 years earlier than the youngest diagnosed relative with ovarian cancer, whichever comes first [31]. Published data clearly indicated that in women at increased risk due to a family history or confirmed mutations in high-penetrance genes such as BRCA1/2, annual screening with CA125 and TVS concurrently or sequentially did not detect early-stage cancers [50, 51]. It is also important to recognize that these surveillance methods have not been shown to reduce ovarian cancer mortality [51]. Therefore, screening at present cannot be considered as a safe alternative strategy to risk-reducing surgery.

In the general populations, low parity, infertility, early menarche, and late menopause have all been associated with an increased risk of ovarian cancer. A meta-analysis of case-control and cohort studies showed that use of oral contraceptives is associated with a 40–50% lifetime risk reduction of ovarian cancer [52, 53]. The risk reduction does not differ between the use of the current low-dose oral contraceptives and the high-dose formulations used in the past (OR, 0.5; 95% CI, 0.3–0.7). A survival benefit from oral contraceptives was achieved with longer use. A 36% risk reduction occurred with an additional 10 years of use (summary relative risk [SRR], 0.64; 95% CI, 0.53–0.78), and the benefit can last for 15 years after discontinuation of use.

In the high-risk populations, a meta-analysis of 18 case-control and retrospective cohort studies in BRCA1/2 mutation carriers who used oral contraceptives identified a significant reduction in the risk of ovarian cancer (SRR, 0.50; 95% CI, 0.33–0.75) [54] and by as much as 44%–60% [55, 56]. There is a positive correlation between the duration of oral contraceptive use (regardless of the continuous and discontinuous use) and the degree of ovarian cancer protection, quantified as a 5%–13% risk reduction per year [57–59]. Therefore, in the general populations and the BRCA mutation carriers, women might consider taking oral contraceptives to

reduce their ovarian cancer risk in clinical decision-making. Since risk-reducing pharmacologic options provide improved prevention strategies for high-risk women who delay or decline RRSO, alternative ovarian cancer risk-reduction strategies should be discussed.

In addition, a systematic review on a correlation between the use of oral contraceptives and breast cancer risk in the general population has been carried out and concluded that there may be a small increased risk of breast cancer (OR, 1.08; 95% CI, 1.00–1.17) and thrombosis [60]. The results indicated that the risk of breast cancer may vary considerably based on several factors: age at which oral contraceptive commenced (under the age of 30), the length of oral contraceptive use (an increased risk with use beyond 5 years and the current recommendation of short-term use), time since cessation of oral contraceptives, and formulation of oral contraceptives (an increased risk occurred with formulations used before 1975, but this risk was not found for the more recent formulations) [61–65]. There was no significant association between modern oral contraceptive use and breast cancer risk (SRR, 1.13; 95% CI, 0.88–1.45). There have been conflicting data demonstrating the efficacy of oral contraceptive use on the risk of breast cancer in BRCA mutation carriers [56, 61, 65]. Importantly, a recent meta-analysis demonstrated a significant ovarian cancer risk reduction and no increased breast cancer risk with oral contraceptive use by BRCA mutation carriers [63]. The management guidelines for cancer screening and risk-reducing options will continue to be updated.

4.5 Prevention of Breast Cancer

4.5.1 Risk-Reducing Surgical Options

Risk-reducing bilateral mastectomy (RRM) decreases breast cancer risk by up to 95% in BRCA mutation carriers [66]. A significant impact on life expectancy gain is derived from RRM in the fourth decade of life. In clinical practice, individualized recommendations should be made based on the critical role for pretest genetic counseling, the age at which family members developed breast cancer, and addressing psychosocial concerns after surgery.

4.5.2 Risk-Reducing Pharmacologic Options

Although limited data exist on their efficacy in BRCA mutation carriers, chemoprevention with selective estrogen-receptor modulators (tamoxifen and raloxifene) and aromatase inhibitors (e.g., exemestane) reduced breast cancer incidence [67]. In contrast, a case-control study of BRCA1/2 mutation carriers with breast cancer demonstrated a strong protective effect of tamoxifen against contralateral breast cancer in both BRCA1 (OR, 0.5) and BRCA2 (OR, 0.4) mutation carriers, irrespective of estrogen-receptor status of the initial breast cancer [68]. In a subset analysis of another study showed that tamoxifen reduced invasive breast cancer by 62% in

BRCA2 mutation carriers, but not in BRCA1 mutation carriers [67]. Tamoxifen also increased the risks of endometrial cancer, thromboembolic events, stroke, cataracts, and others (vasomotor symptoms, leg cramps, vaginal discharge, and irritation) [69]. The use of tamoxifen should be approached with caution.

4.6 Ovarian Cancer Screening in the Japanese Population

Japanese patients presented with higher incidence of ovarian clear cell carcinoma that is the second-most common type of EOC in Asia. Endometriosis serves as a precursor of EAOC, especially of the clear cell and endometrioid subtypes. More than half of the EOC were attributable to EAOC in Japan. The ovarian cancer screening program in Japan would be to predict malignant transformation of endometriosis and identify women with EAOC in an early stage, which may improve survival.

Recent studies have indicated the clinical utility of measurement of cyst fluid iron, hemoglobin (Hb) species, and their concentrations for the early prediction of malignant transformation of endometriosis [70]. EAOC cyst fluids had much lower levels of total iron, heme iron, and free iron compared with endometriotic cyst samples. Iron-related compounds may serve as predictive biomarkers for early diagnosis of malignant transformation for women with endometriosis. Possible biomarkers have also been extensively investigated in EAOC and endometriosis: methemoglobin (metHb) and oxyhemoglobin (oxyHb) are one of the most abundant Hb species in benign endometriotic cysts and EAOC cysts, respectively [71]. The metHb/oxyHb ratio had a sensitivity, specificity, positive predictive value, and negative predictive value of 62.5%, 100.0%, 100.0%, and 92.1%, respectively, and may predict subsequent malignant transformation from endometriosis to EAOC. Iron concentration and Hb species in the cyst are the central diagnostic indicators for malignant transformation of endometriosis. Therefore, they can be helpful in the delineation of malignant tissue from nonneoplastic tissue.

Several imaging technologies have evolved into a clinically translatable platform to measure the cyst fluid concentrations of iron and Hb species: the potential techniques include conductance methods using electrical admittance plethysmography, combination near-infrared (NIR) vascular imaging/spectrophotometry, NIR transmission spectroscopy, steady-state visible and NIR diffuse reflectance spectrophotometry, or optoacoustic spectroscopy based on pulse-echo ultrasound [72]. The Hb values may be estimated by the portable devices across a wide Hb spectrum, including the Rad-87™ pulse CO-Oximeter with Rainbow Set technology (Masimo), Haemospect® (MBR Optical Systems), or a transcutaneous spectroscopic device (Mediscan 2000, MBR Optical Systems, Wuppertal, Germany) by noninvasive and contact procedures [73, 74]. A truly noninvasive device with the miniaturization and simplification of actuators has to be adopted as a standard of care in a clinical practice. These devices' performance would provide adequate potential for screening purposes in malignant transformation of endometriosis, more than half of the patients diagnosed with ovarian cancer in Japan.

4.7 Discussion

This review focused on the screening and prevention of ovarian cancer. It is a general consensus that at present no population-based screening test is recommended for ovarian cancer detection in the general populations and the high-risk groups. Although annual screening may be associated with the limited stage shift at ovarian cancer detection in the UK (the UKCTOCS study) [24, 25] but no stage shift in the USA (the PLCO study) [22, 23] and Japan (the Shizuoka study) [21], there are no established data in these randomized controlled trials that the mortality of ovarian cancer can be decreased by the screening arm. Interestingly, the results of the UKCTOCS study showed that annual multimodal screening significantly reduced ovarian cancer mortality after excluding either deaths in the first 7 years after randomization or prevalent cancers [24, 25]. However, exclusion of all deaths in years 0–7 is hard to understand: the impact of multimodal screening on ovarian cancer mortality may not be established. In the Shizuoka study, stage shift was found in the screening group, more stage I ovarian cancers in the screened group (63%) compared to the control (38%), but this did not reach statistical significance [21]. However, this screening mainly detected at an earlier stage the less aggressive and low-grade cancers, which include EAOC (clear cell [33%] and endometrioid [19%] subtypes) [21]. These data theoretically imply that ovarian cancer mortality may be lowered by annual screening of endometriosis in Japan [75].

This review also discussed the available data on the risk-reducing surgical options and chemoprevention strategies in ovarian cancer. Up to now, management of this condition relied mostly on surgical treatments. The use of preventive surgery can dramatically reduce ovarian and breast cancer risks and mortality in women who carry the BRCA1 and BRCA2 mutations. Although prophylactic RRSO and RRM reduced cancer incidence compared to chemoprevention or surveillance, many women who are at risk for BRCA1/2 mutations delay or decline prophylactic surgery [37, 38]. In general, 10%–50% opted for prophylactic surgeries in asymptomatic women with BRCA1/2 mutations. The factors that influence decisions to undergo or decline prophylactic surgery are age, having children, country, race, genetic testing itself, risk perceptions, cancer witnessed in family members, family obligations, concerns about fertility and menopause, psychological factors, and fear of surgical complications. Women must balance short- and long-term benefits of anxiety reduction against a series of potential complications of surgery.

Oral contraceptives are proposed as a chemoprevention agent for ovarian cancer. Chemoprevention is an attractive option to prevent the disease in the general populations and high-risk populations. Chemoprevention contributes to reducing ovarian cancer deaths, with a special attention on the breast cancer risk. Breast cancer risk may vary by age at first oral contraceptive use, duration of use, intervals from the last use, and oral contraceptive formulation.

We conclude that since there is no effective screening for ovarian cancer in the general population and high-risk groups, screening at present cannot be considered as a safe alternative strategy to risk-reducing surgery in the BRCA mutation carriers. Clinicians are recommended to encourage high-risk women

who delay or decline risk-reducing surgery to discuss risk-reducing pharmacologic options in order to prevent ovarian cancer progression without elevation of breast cancer risk.

Conclusion

The aim of this study is to review clinical studies for organizing a screening and prevention program for ovarian cancer. At present, there is no effective screening for ovarian cancer. Clinicians are recommended to encourage high-risk women who delay or decline risk-reducing surgery to discuss risk-reducing pharmacologic options in order to prevent ovarian cancer progression without elevation of breast cancer risk.

Acknowledgments Grant support: Supported by Grant-in-aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan to the Department of Obstetrics and Gynecology, Nara Medical University (H. Kobayashi).

Conflict of interest The author declares no conflict of interest.

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