Chapter 2

Screening and prevention of ovarian cancer

Prevention of ovarian carcinoma

Oral contraceptive pills

Use of oral contraceptive pills (OCPs) has been associated with a significant reduction in the risk of ovarian cancer. Specifically, after one year of use, the risk has been shown to decrease by 10–12%, and by approximately 50% after five years of use. The Cancer and Steroid Hormone (CASH) study researchers reported that the reduction in ovarian cancer risk was the same irrespective of the type or amount of estrogen or progestin in the OCP [1]. Follow-up analysis of CASH data have indicated that formulations with high levels of progestin are associated with a lower risk of ovarian cancer compared with formulations with low progestin concentrations [2]. The Steroid Hormones and Reproductions (SHARE) study was noteworthy for finding no difference in ovarian cancer risk between androgenic and nonandrogenic pills [2]. Women harboring genetic mutations that predispose them to the development of breast and ovarian cancer (ie, the *breast cancer susceptibility gene 1* and *2* [*BRCA1* and *BRCA2*] mutation carriers) also seem to benefit from a reduction in risk of ovarian cancer through the use of OCP [3].

Risk-reducing bilateral salpingoophorectomy

Risk-reducing bilateral salpingoophorectomy (rrBSO) should be considered for women at the highest risk of epithelial ovarian and fallopian tubal

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cancer [4–6]. Among patients with *BRCA1* gene mutations, the lifetime risk of ovarian cancer is approximately 40%, and in those with *BRCA2* gene mutations the lifetime risk is approximately 20% [7]. Finally, women with a strong family history of either ovarian or breast cancer who have not undergone genetic testing may carry a deleterious mutation and can be presumed to be at higher-than-average risk. For this reason they should also be considered candidates for rrBSO. An additional benefit among *BRCA* mutation carriers is that rrBSO will reduce the risk of breast cancer by 30 to 75%. In most situations, rrBSO is typically deferred until women have completed childbearing.

It has been estimated that approximately 15% of patients with Lynch syndrome are at risk for ovarian cancer. These patients also have a lifetime risk of 60% for developing endometrial cancer and therefore risk-reducing surgery includes hysterectomy. The risk of breast cancer in Lynch syndrome is controversial [4–6].

The finding of occult fallopian tubal cancers in women who have undergone rrBSO suggests that some presumed ovarian cancers can initiate in the fallopian tubes. Due to microscopic rests of residual ovary, occult pre-existing carcinomatosis at the time of prophylactic surgery, and/or multifocal origin of peritoneal tissue, after rrBSO, the risk of developing serous carcinoma of the peritoneum has been reported to be in the range of 1.7–4.3% [4–6].

The technique of rrBSO and pathologic processing should include:

1. Bilateral salpingoophorectomy with removal of the entire fallopian tube
2. Cytologic examination of peritoneal washings
3. Random peritoneal and omental biopsies along with a biopsy of any suspicious lesion
4. Serial sectioning of the entire fallopian tube and ovaries at 2 mm intervals and microscopic examination of all sections

Gynecologic Oncology Group protocol 0199: risk-reducing bilateral salpingoophorectomy component

Gynecologic Oncology Group (GOG) protocol 0199 is a non-randomized trial that enrolled women at a high risk of developing ovarian cancer

(ie, *BRCA* mutation carriers or strong family history of ovarian cancer) [8,9]. It has been designed to compare rrBSO at enrollment with serial transvaginal ultrasonography and cancer antigen 125 (CA-125) screening (Risk of Ovarian Cancer Algorithm [ROCA]; see below). All enrolled patients had a baseline CA-125 and a transvaginal ultrasound performed, and then chose to have either rrBSO or continue to be screened at 3-month intervals with the ROCA evaluation. Pathologic review of the 966 prophylactic surgical specimens revealed four pre-invasive tubal cancers and 20 invasive pelvic cancers, involving exclusively the ovary, fallopian tube, or inner peritoneal lining of the body. Of these pelvic cancers only 12 were detected microscopically but all 20 of the cancers were serous carcinomas. Overall, the prevalence of serous pelvic cancers in these asymptomatic women with *BRCA* mutations was 3.2% as compared with 0.5% among those patients who did not have a *BRCA* mutation but had strong family history of breast or ovarian cancer. Interestingly, 515 patients had their uterus removed at the time of removal of the ovaries and six endometrial cancers were also found [8,9]. It is not clear whether these cases of endometrial cancer were sporadic or related to *BRCA* deficiency, but typically endometrial cancers present with bleeding.

Screening for ovarian carcinoma

There are no validated tools that can be used to screen for ovarian cancer in the general population. Neither serum testing for CA-125 alone or in combination with transvaginal pelvic ultrasonography has convincingly succeeded in diagnosing early stage ovarian cancer or decreasing mortality from the disease.

Cancer antigen 125

CA-125 was discovered in 1981 by Bast et al [10]. Although it is the only US Food and Drug Administration (FDA)-approved biomarker for ovarian cancer detection, it is only expressed in approximately 75% of cases, and in particular in the subtype of ovarian cancer called serous carcinoma. It is not expressed by mucinous and other ovarian carcinomas. Additional shortcomings of CA-125 include a lack of sensitivity for detecting early stage ovarian cancer and the potential presence

of this protein at abnormally high levels in many different benign (ie, non-cancerous) gynecologic and non-gynecologic conditions [10]. For these reasons, CA-125 is not a suitable screening test for ovarian cancer in the general population of women and the search for more sensitive and informative biomarkers continues. Accepted uses of CA-125 include: (1) helping to determine whether a pelvic mass is malignant; (2) assisting in determining whether a cancer of unknown primary origin has arisen from the ovary; (3) monitoring response of ovarian cancer to systemic chemotherapy; (4) carrying out surveillance of patients treated for ovarian cancer who are in remission; and (5) screening for ovarian cancer in high-risk populations (ie, patients with a strong family history or *BRCA* mutation carriers).

Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial

The objective of the ovarian component of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial was to estimate whether screening reduces mortality from ovarian cancer in healthy women between the ages of 55–74 years who still have their ovaries [11]. A total of 34,261 women were enrolled onto this trial and were randomly assigned to either no screening interventions or to yearly transvaginal ultrasounds plus CA-125. Eighty-nine patients were diagnosed with ovarian cancer in this study, of which 60 (ie, 67%) were detected through screening with ultrasound plus CA-125. However, 72% of the screen-detected cases were late stage ovarian cancers (ie, stage III and IV). For each case of ovarian cancer discovered, 20 women underwent surgery, meaning that 19 patients underwent surgery for benign conditions for every one case of ovarian cancer diagnosed. These results were initially reported in 2009 [10].

Two important updates from the PLCO study have been published. In 2011, Buys et al compared the mortality rates due to ovarian cancer between the women who did not undergo screening and those who did [12]. In this analysis, the investigators reported that the death rates from ovarian cancer did not significantly differ between the two groups. This means that although more ovarian cancers were found in women

assigned to the group that received yearly ultrasounds plus CA-125, because most of these screen-detected cases were advanced stage cases, the screening did not result in a significantly diminished death rate from ovarian cancer. Screening resulted in over 3000 false positive results and a total of 1080 surgeries, the great majority of which were for benign conditions as discussed earlier [12]. Additionally, 15% of patients who underwent surgery suffered serious surgical complications. Clearly, a more sensitive screening tool is needed that can detect ovarian cancer in its earliest stages and which is better able to discriminate between benign and cancerous conditions.

In 2012, Moore et al studied blood samples taken from patients on the PLCO trial and reported that approximately 62% of the 65 patients who had CA-125 data available in blood samples collected less than a year before their ovarian cancer diagnosis had an elevated CA-125 level. These scientists probed these same blood samples for seven other promising biomarkers but even when combined with CA-125, this panel of markers was not found to be more sensitive than CA-125 alone in detecting ovarian cancer [13].

Development of the Risk of Ovarian Cancer Algorithm

In a strategy to improve the sensitivity of CA-125 in detecting ovarian cancer, the ROCA was designed (Figure 2.1) [14]. The basic concept is to use the CA-125 level of a woman as the yardstick (or baseline level) against which any fluctuations or changes in the CA-125 over time can be measured. Risk estimates or a ROCA score of developing ovarian cancer can then be provided by inputting these CA-125 changes into a mathematical model that includes the age of the woman. Although CA-125 can be abnormally elevated in non-cancerous conditions, the hypothesis is that CA-125 levels should steadily increase over time in a woman who is ultimately going to develop ovarian cancer, whereas the CA-125 levels would be expected to remain typically stable or even decrease in those with non-cancerous conditions (eg, endometriosis). Theoretically then, by monitoring the ROCA score carefully the disease may be intercepted before it starts to spread, leading to higher cure rates. Several important ROCA studies are ongoing.

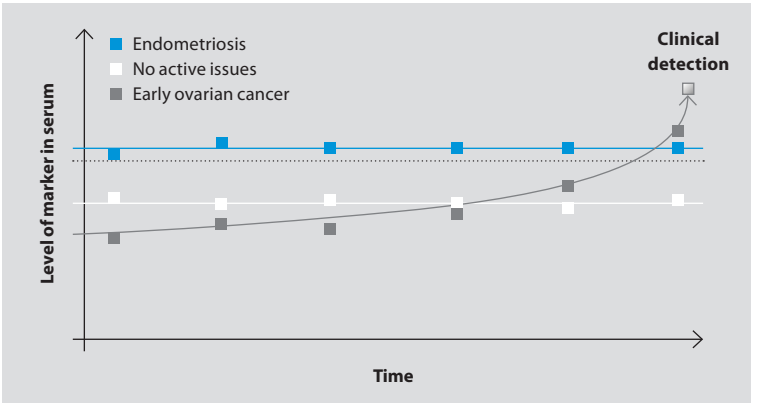

Figure 2.1 The Risk of Ovarian Cancer Algorithm (ROCA) showing the relative length of time for early ovarian cancer to become clinically detectable. Adapted from © American Association for Cancer Research, 2002. All rights reserved. McIntosh et al [15].

United States Risk of Ovarian Cancer Algorithm study (general population)

The ROCA study in the United States is being performed by the National Cancer Institute's Cancer Genetics Network, the Early Detection Research Network, and the Ovarian Specialized Program on Research Excellence. In this single arm, prospective, multicenter screening study, 4051 women (50–74 years) with no significant family history of breast or ovarian cancer underwent an annual CA-125 blood test. Based on the ROCA result, women were triaged to the next annual CA-125 test (low risk), to repeat the CA-125 test in 3 months (intermediate risk), or to a transvaginal ultrasound study with referral to a gynecologic oncologist (high risk). Based on the results of the clinical findings and ultrasound result, the gynecologic oncologist then made the decision whether or not to proceed with surgery [16].

The average annual rate of placement of study participants into the intermediate risk group was 5.8%, while the annual rate of referral for transvaginal ultrasonography and consultation with a gynecologic oncologist was 0.9% [16]. Ten women underwent surgery, with four invasive ovarian cancers (one with stage IA disease, two with stage IC disease, and one with stage IIB disease), two ovarian tumors of low malignant potential (both stage IA), one stage I endometrial cancer,

and three benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval [CI] 12.2, 73.8) for detecting invasive ovarian cancer. The specificity was 99.9% (95% CI 99.7, 100.0) [16]. All four women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA-125 test values prior to rising CA-125 levels.

United Kingdom Risk of Ovarian Cancer Algorithm Study (general population)

These results are very consistent with another ROCA study being performed in the United Kingdom (the UK Collaborate Trial of Ovarian Cancer Screening) [17]. In this second study, over 200,000 postmenopausal women (ages 50–74 years) have been randomly assigned to one of three arms: (1) no screening; (2) annual CA-125 blood tests with ROCA followed by transvaginal ultrasound if the ROCA is worrisome; and (3) screening with transvaginal ultrasound only on a yearly basis. In this study, the ROCA led to the detection of 16 ovarian or fallopian tube cancers in the early stages (ie, stage I–II) [17].

Risk of Ovarian Cancer Algorithm studies are consistent

The United States and United Kingdom ROCA studies are consistent with one another. The specificity for both studies is 99.8%. In addition, the positive predictive value of the United States study of 37.5% is also identical to the positive predictive value of 37.5% reported for the United Kingdom study [16,17]. These studies make it clear that ROCA can detect ovarian cancers at an early stage in the general population; however, survival data are not yet mature enough to allow us to determine whether ROCA can reduce the mortality rates from ovarian cancer.

United Kingdom Risk of Ovarian Cancer Algorithm study (high-risk population)

The United Kingdom Familial Ovarian Cancer Screening Study (UKFOCSS) has had two phases. In phase I, Rosenthal et al showed that annual transvaginal ultrasound and CA-125 screening in women at high risk of ovarian and fallopian tube cancer lacked sensitivity for early stage disease but may

result in improved optimal debulking rates when patients were taken to surgery [18]. It was thought that more frequent screening might provide greater benefits, so a phase II program was launched [18]. Among the modifications in the phase II program were screening every 4 months, implementation of a web-based system notifying physicians when additional testing and/or referral was required, and incorporation of the ROCA scores. Eligibility criteria included >10% lifetime risk of ovarian cancer, age >35 years, and declined rrBSO. For 5 years, 4531 women at high risk of ovarian and fallopian tube cancer were recruited and screened at 42 UK centers. The median age was 45.5 years. CA-125 tests were analyzed every 4 months through ROCA; transvaginal sonography (TVS) was analyzed annually.

Roesenthal et al reported that data from more frequent than annual screening constitute further evidence of a beneficial effect on success of debulking surgery, which may translate into improved survival. Sixteen incident cases of ovarian cancer were detected, of which eight (50%) were stage I or II. The calculated sensitivity ranged from 75–100%, with specificity of 96.1% and positive predictive value (PPV) of 13% [19]. Interestingly, four of the 16 patients with ovarian cancer had normal pelvic ultrasonography and were identified based on an abnormal ROCA. The investigator suggested that potentially avoidable delays in physician referral were reduced by using the internet notification system. This was possibly because the trial did not mandate serial sectioning of the fallopian tubes and ovaries among those patients who ultimately underwent rrBSO (n=653). There was a low rate of occult carcinoma in this high-risk population (n=4; 0.6%) [19].

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