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Evidence Summary Report 4-6b EDUCATION AND INFORMATION 2014

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Screening High-risk Women for Ovarian Cancer

Report Date: August 3, 2004

An assessment conducted in September 2014 put Evidence Summary (ES) 4-6b in the Education and Information section. This means the recommendations will no longer be maintained but may still be useful for academic or other information. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

This ES consists of a Summary and a Full Report and is available on the CCO website at the PEBC Gynecologic Cancer Disease Site Group page

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Screening High-risk Women for Ovarian Cancer
Evidence Summary Report #4-6b- EDUCATION AND INFORMATION 2014

Report Date: August 3, 2004

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base practice recommendations.

SUMMARY

Question

Is there a role for screening women who are at high risk for developing ovarian cancer (see Target Population for definition of high risk)? The outcome of interest was the performance of screening tests assessed in terms of predictive values, sensitivity and specificity, stage of screen-detected disease at diagnosis, and survival.

Target Population

This evidence summary applies to women who are at high risk for developing ovarian cancer. The definition for high risk is adapted from the American Society of Clinical Oncology definition of risk for ovarian cancer. Women at high risk of ovarian cancer have at least one of the following:

- First-degree relative diagnosed with ovarian cancer before age 40
- First-degree relative diagnosed with breast and ovarian cancer (one cancer diagnosis before age 50)
- Two or more first- and second-degree relatives (of same lineage) with ovarian cancer
- Two or more first- and second-degree relatives (of same lineage) with breast cancer and one relative with ovarian cancer
- One first- or second-degree relative with breast cancer before age 40 and one first- or second-degree relative with ovarian cancer before age 50 (of same lineage).
- Two or more first-and second-degree relatives (of same lineage) diagnosed with breast cancer before age 50.
- Two or more first- and second-degree relatives (of same lineage) diagnosed with breast cancer, one before age 40

Opinions of the Gynecology Cancer Disease Site Group

The lack of sufficient high quality evidence precludes definitive recommendations being made. Instead, the Gynecology Cancer Disease Site Group offers the following opinions, based on the evidence reviewed:

- Studies are inadequate to establish benefits from screening the population of women who are at risk for developing ovarian cancer.
- The population of women who are at high risk for developing ovarian cancer has not been studied adequately enough to establish that screening is beneficial.

- More long-term studies of women who are at high risk for developing ovarian cancer need to be conducted in order to determine if there is any benefit from screening.
- Women may experience distress about their perceived risk of ovarian cancer regardless of their familial ovarian cancer risk. Practitioners should acknowledge this distress and educate women about their risk of developing ovarian cancer and the effectiveness of available screening tests.
- There are no high-quality randomized controlled trials examining the role of screening women at high risk for developing ovarian cancer. Such trials would be of benefit to health care providers and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

Methods

Entries to MEDLINE (1995 to September 2003), CANCERLIT (1983 to October 2002), and Cochrane Library (2003, Issue 3) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology were systematically searched (1997 to 2003) for evidence relevant to this evidence summary report.

Evidence was selected and reviewed by two members of the Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This evidence summary report has been reviewed and approved by the Gynecology Cancer Disease Site Group, which comprises gynecologic oncologists, medical oncologists, radiation oncologists, an oncology nurse, a pathologist, and patient representatives.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Key Evidence

- One systematic review and 11 prospective studies and one retrospective study described screening women at high risk for developing ovarian cancer.
- Four screening interventions for the detection of ovarian cancer were studied: concurrent CA125 and ultrasound (six prospective studies and one retrospective study); sequential CA125 and ultrasound (two prospective studies); ultrasound with colour Doppler imaging (one prospective study); and ultrasound alone (two prospective studies).
- No screening intervention was found to be superior to another in terms of detection rates for ovarian cancer.
- Of the 22,083 women screened in all the studies, 52 cases of ovarian cancer were detected (0.2%).
- The number of patients who are screened who test positive and who truly have ovarian cancer ranges from 0-50%. The concern is the ramifications for those who test positive, because a significant number will not have ovarian cancer.
- Women who are at high risk for developing ovarian cancer tend to underestimate their risk of developing ovarian cancer, as opposed to women who are not at high risk, who tend to overestimate their risk of developing ovarian cancer.

Future Research

In addition to assessing the impact of screening on survival, future research needs to focus on the ideal sequencing of screening tests. More tumour markers need to be identified that are more accurate than cancer antigen 125 at detecting ovarian cancer. Longitudinal screening algorithms using novel tumour markers also need to be developed because cancer antigen 125 algorithms are computationally intensive.

Related Evidence Summaries

Practice Guidelines Initiative's Evidence Summary Reports:

- #4-4 *Management Options for Women with a Hereditary Predisposition to Ovarian Cancer*
- #4-6a *Screening Postmenopausal Women for Ovarian Cancer*

For further information about this evidence summary report, please contact Dr. Michael Fung Kee Fung, Chair, Gynecology Cancer Disease Site Group, Ottawa General Hospital, 50 Smyth Road, Ottawa, Ontario; TEL 613-737-8560; FAX 613-737-8828.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.

Visit www.cancercare.on.ca/
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PREAMBLE: About Our Evidence Summary Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle.[1]

An evidence summary report is a systematic overview of the best evidence available on a specific clinical question when there is insufficient high-quality evidence on which to base a practice guideline. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. For example, the evidence comes from uncontrolled studies, from studies with control groups that are not relevant to current practice in Ontario, or from subgroup analyses, or the evidence consists solely of preliminary results from ongoing trials. The PEBC will monitor the scientific literature and will develop a practice guideline on this topic when more evidence becomes available.

This evidence summary report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives, and CCO executives. Formal approval of an evidence summary by the Coordinating Committee does not necessarily mean that the evidence summary has been adopted as a practice policy of CCO. The decision to adopt an evidence summary as a practice policy rests with each regional cancer network, which is expected to consult with relevant stakeholders, including CCO.

Reference:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:

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FULL REPORT- ARCHIVED 2014

I. QUESTION

Is there a role for screening women who are at high risk for developing ovarian cancer (as defined by the American Society of Clinical Oncology [ASCO])? The outcome of interest was the performance of screening tests assessed in terms of predictive values, sensitivity and specificity, stage of screen-detected disease at diagnosis, and survival.

II. CHOICE OF TOPIC AND RATIONALE

Epithelial ovarian cancer is the sixth most common female malignancy after cancers of the breast, lung, colon, and uterus and non-Hodgkin's lymphoma. It is the fourth leading cause of cancer deaths among this group and the leading cause of gynecologic cancer mortality. In Ontario, 980 new cases and 570 deaths from ovarian cancer were estimated to have occurred in 2001 (1), a case fatality ratio of **.**58.

Hereditary ovarian cancer was first described by Lynch more than 20 years ago (2). The BRCA1 gene was cloned in 1993, and, the BRCA2 gene was cloned subsequently in 1995. Both genes have been linked to ovarian and breast cancer. Four large case series, which tested 998 women unselected for family history, analyzed the risk of ovarian cancer from BRCA1 and BRCA2 (3). The reported analysis estimated that carriers of BRCA1 germline mutations have an average cumulative risk of developing ovarian cancer by age 70 of 39% (95% confidence interval [CI] 22-51%), and those with a BRCA2 mutation have an average cumulative risk by age 70 of 11% (95% CI 4.1-18%) (3) (see Table 1). At least 10% of ovarian cancers are hereditary, and as many as 16% of serous histology cancers are linked to BRCA1 or 2 germline mutations (4).

Table 1. Rates of ovarian cancer according to gene mutations BRCA1 or BRCA2 (3,5).

Gene mutation	All cases of invasive ovarian cancer	All cases of serous ovarian cancer	Inherited cases	Risk to age 70
No mutation	88%	84%	NA	1.4%
BRCA1	7%	9.5%	60%	39%
BRCA2	5%	6.5%	40%	11%

Note: NA, not applicable

The risk of developing ovarian cancer varies with age, depending on the gene. For those with BRCA1 mutations, the lifetime risk of developing ovarian cancer is higher at a younger age (45-50 years) than for those with BRCA2 mutations (who develop ovarian cancer on average at 55-60 years). This age difference has implications for the timing of screening initiation and for other preventative strategies. This evidence summary uses the ASCO definition of high risk, which is based on family history of ovarian or breast cancer (Table 2). Essentially, women considered high risk according to the ASCO definition have two or more first- degree relatives with ovarian or breast cancer, or they have one first-degree relative with ovarian cancer who is less than 40 years.

Table 2. ASCO definitions of risk for ovarian cancer (based on family history).

Risk	Family History
High risk	• First-degree relative diagnosed with ovarian cancer before age 40 • First-degree relative diagnosed with breast and ovarian cancer (one cancer diagnosis before age 50) • Two or more first- and second-degree relatives (of same lineage) with ovarian cancer • Two or more first- and second-degree relatives (of same lineage) with breast cancer and one relative with ovarian cancer • One first- or second-degree relative with breast cancer before age 40 and one first- or second-degree relative with ovarian cancer before age 50 (of same lineage). • Two or more first-and second-degree relatives (of same lineage) diagnosed with breast cancer before age 50. • Two or more first- and second-degree relatives (of same lineage) diagnosed with breast cancer, one before age 40
Increased risk	• First-degree relative diagnosed with ovarian cancer
Average risk	• No first-degree relatives with history of ovarian cancer

Andersen et al's study (6) on risk perception reported that women at low risk for developing ovarian cancer overestimated their risk, leading to increased anxiety levels. On the other hand, women with a high risk of developing ovarian cancer often underestimated their risk, which can potentially lead to denial and avoidance behaviour. This finding is important to the topic of screening: if high-risk women do not seek screening, screening programs will not be effective.

Women at high risk for developing ovarian cancer have options for decreasing their lifetime risk of the disease, including the use of oral contraceptives, tubal ligation, and prophylactic surgery (7,8). However, these options have limitations. For example, some women may choose not to use oral contraceptives because they are already at increased risk for breast cancer and do not wish to increase that risk even slightly. In addition, some women wish to delay prophylactic surgery until they have completed their families. In the interim, the use of screening tests (cancer antigen 125 [CA 125] and/or pelvic ultrasound) has been suggested.

Currently, the Ontario Cancer Genetics Network recommends informing high-risk women about screening. In Ontario, both periodic transvaginal ultrasonography and serial CA 125 serum testing are being used, individually or in combination, for women who request screening. The potential causes of an elevated CA 125 result are listed in Appendix 1.

The aim of any screening test is to maximize accuracy through sensitivity and specificity. It is important to understand the likelihood of false positive results and the subsequent implications for affected individuals. False-positive results for ovarian cancer can lead to surgery; thus, the rate of false positives for a screening test needs to be weighed against the benefits of the test. If the screening tests are failing to detect disease or are not detecting early-stage disease, then the effectiveness of screening is limited (staging criteria are listed in Appendix 2).

The Gynecology Cancer Disease Site Group (DSG) has recently developed an evidence summary on screening women in the general population for ovarian cancer (Evidence Summary #4-6a: http://www.cancercare.on.ca/pdf/full4_6aes.pdf). In that evidence summary, the Gynecology Cancer DSG reported that there is insufficient evidence at this time to warrant the routine screening of women in the general population for ovarian cancer, because the incidence of ovarian cancer in the general population is low and current screening tests are not sensitive or specific enough to identify disease. Instead, the Gynecology Cancer DSG chose to develop an evidence summary focused specifically on women at a high risk for ovarian cancer to determine if screening in this population is more appropriate, because the disease incidence is significantly higher in these women than in the general population.

Principles of Screening Definitions (Table 3)

- True positive: women with a positive screening test and confirmed ovarian cancer,
- False-positive: women with a positive screening test and no confirmed ovarian cancer,
- True-negative: women with a negative screening test and no confirmed ovarian cancer,
- False-negative: women with a negative screening test and confirmed ovarian cancer,
- Positive predictive value (PPV): the proportion of women with a positive screening test who have confirmed ovarian cancer [i.e., true positives/(true positives + false positives)]

Table 3. Principles of screening.

	Confirmed ovarian cancer	No confirmed ovarian cancer
Positive test for ovarian cancer	TRUE POSITIVE	FALSE POSITIVE
Negative test for ovarian cancer	FALSE NEGATIVE	TRUE NEGATIVE

- Sensitivity: the proportion of women with ovarian cancer found by screening (i.e., true positives/[true positives + false negatives]), i.e., the chance that a person with cancer has a positive test.
- Specificity: proportion of women who do not have ovarian cancer who test negative (i.e., true negatives/[true negatives + false positives]), i.e., the chance that a person without cancer has a negative test.

III. METHODS

Evidence Summary Development

This evidence summary report was developed by the Practice Guidelines Initiative (PGI) of Cancer Care Ontario's Program in Evidence-based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (9). Evidence was selected and reviewed by two members of the PGI's Gynecology Cancer DSG and methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict of interest information. There were no conflicts of interest regarding this evidence summary reported by the Gynecology Cancer DSG members.

The evidence summary report is a convenient and up-to-date source of the best available evidence on screening high-risk women for ovarian cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. In contrast to the practice guidelines, the body of evidence in an evidence summary is less mature and is comprised of data primarily from non-randomized controlled trial data or data available only in abstract form. As this fact precludes the development of definitive recommendations, opinions of the DSG are offered instead. The report is intended as information for individuals and groups to use in making decisions and policies where the evidence is uncertain. The PGI is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

External review by Ontario practitioners is obtained for all evidence summary reports through a mailed survey consisting of items that address the quality of the evidence summary report, the interpretation of the available evidence, and whether there is a need to develop an evidence-based practice guideline when sufficient evidence is available. Final approval of the evidence summary report is obtained from the Practice Guidelines Coordinating Committee (PGCC).

The PGI has a formal standardized process to ensure the currency of each evidence summary report. This process consists of the periodic review and evaluation of the scientific literature and, where appropriate, integration of this literature with the original evidence summary.

Literature Search Strategy

MEDLINE (1995 through September 2003), CANCERLIT (1983 through October 2002), Cochrane Library (2003, Issue 3), and PRE-MEDLINE databases were searched for systematic reviews and clinical trials. Reference lists of papers and review articles were scanned for additional citations. Abstracts from the 1997 to 2003 meetings of American Society of Clinical Oncology were searched for additional citations. The Canadian Medical Association (CMA) Infobase (http://mdm.ca/cpgsnew/cpgs/index.asp), the National Guidelines Clearinghouse (http://www.guideline.gov/), and other Web sites were searched for existing evidence-based practice guidelines.

The following text words and medical subject headings (MeSH) were used: ovary, ovarian, cancer, carcinoma, neoplasms, high risk, hereditary, genetic, screening, and mass screening (as an exploded MeSH term). Search terms related to study design and publication type, used to search the MEDLINE and CANCERLIT databases, included clinical trial (text word and publication type), clinical trials (as an exploded MeSH term), meta-analysis (text word and publication type), and systematic review.

Inclusion Criteria

Full papers or abstracts were selected for inclusion in this evidence summary if they met all the following criteria:

1. reported clinical trials (randomized controlled trials, comparative cohort studies or single-cohort studies) or systematic reviews of clinical trials,
2. evaluated tests to detect ovarian cancer,
3. included asymptomatic women at high risk for developing ovarian cancer (Appendix 1 outlines ASCO's definitions of risk for ovarian cancer),
4. reported rates of confirmed ovarian cancer.

Exclusion Criteria

Studies that evaluated the screening of patients with symptoms suggestive of ovarian cancer or women undergoing immediate gynecologic surgery were excluded. Studies where the majority of participants were women who were not at high hereditary risk for ovarian cancer were also excluded. Studies published in languages other than English were excluded.

Synthesizing the Evidence

The cohort studies identified were stratified into four intervention categories according to the interventions used and the sequence: CA 125 followed by ultrasonography, ultrasonography followed by CA 125, ultrasonography alone, and colour Doppler imaging (CDI). To calculate the PPVs for each study, the Gynecology Cancer DSG divided the number of ovarian cancer cases (true positives) by the number of women who underwent surgery due to abnormal test results (true positives + false positives).

IV. RESULTS

Literature Search Results

There were two practice guidelines and one systematic review identified that described the screening of women with a high risk of developing ovarian cancer. In addition, 12 non-comparative studies (one retrospective study) provide the evidence for screening high-risk women for ovarian cancer (Table 4).

Table 4. Details of studies included in evidence summary.

	Number of studies	References
Practice Guidelines	2	(10,11)
Systematic Reviews	1 (+ 1 abbreviated version)	(12,13)
Comparative and non-comparative studies (includes studies from systematic review)		
Concurrent CA 125 and ultrasonography	6 prospective cohort studies 1 retrospective study	(14-18) (19) [a] (20) [a]
Sequential CA 125 and ultrasonography	2 prospective cohort studies	(21) (22) [a]
Ultrasonography plus CDI	1 prospective cohort study	(23)
Ultrasonography alone	2 prospective cohort studies	(24) (25) [a]

[a] Studies that have been published since the publication of the NHS systematic review (13).

Practice Guidelines

In 1994, the American College of Physicians published a clinical guideline on screening for ovarian cancer (10), with the following recommendations:

- "In women with a family history of ovarian cancer in one or more relatives (without evidence of a hereditary cancer syndrome), routine screening with CA 125 or ultrasound in general is not recommended. Women requesting screening should be counselled about their individual risk (considering age, parity, and a history of oral contraceptive pill use), about the potential adverse effects of screening, and about the lack of scientific evidence that deaths from ovarian cancer are decreased by screening. Women and their physicians should consider this information in making individual decisions about screening."
- "For women from a family with the rare hereditary ovarian cancer syndrome, referral for specialist care is recommended."

In 1996, the United States Preventive Task Force issued an evidence-based practice guideline (11) stating that "[t]here is insufficient evidence to recommend for or against the screening of asymptomatic women at increased risk of ovarian cancer."

Systematic Review

The National Health Service (NHS) Centre for Reviews and Dissemination at the University of York (United Kingdom) published a systematic review of study results available in May 1997 (13). The NHS review, which included a larger number of studies than the guideline reports noted above (10,11), was published as a Health Technology Assessment report for the NHS Research and Development Health Technology Assessment Programme (13) and also, in an abbreviated form, in the *British Journal of Obstetrics and Gynaecology* (12).

The NHS review addressed four issues: the effectiveness of screening programs, screening test performance, the potential impact of screening, and screening of higher-risk populations. Only prospective studies where ovarian cancer was confirmed by diagnostic surgery were included in the assessment of effectiveness. Literature on the adverse physical and psychological effects of ovarian cancer screening was also reviewed. Genetic testing for cancer risk was not included as a screening manoeuvre. The NHS reviewers concluded that, in the absence of evidence from randomized controlled trials, no assumptions about the effectiveness of screening programs for women with a family history of ovarian cancer could be made.

The NHS review did not consistently define high risk: only seven of the 11 cohort studies included women specifically with a family history of ovarian cancer. The NHS review included the study by Andolf et al (24) among the high-risk studies, even though the only eligibility criterion was that the women be between the ages of 40 and 70 years; there was no requirement for a positive family history of ovarian cancer. Despite some limitations, the NHS review is the most thorough systematic review to date.

The NHS review pooled data from eight cohort studies (14-18,21,23,24) and reported that 21 ovarian cancers were found among 4,551 women screened with ultrasound (alone or accompanied by CA 125). Fifty-seven percent (95% CI, 34% to 78%) of the ovarian cancers detected by ultrasound-based screening were diagnosed at stage I. In the six studies that were restricted to women with a family history of ovarian cancer (14-18,21), there were 15 cancers found among 3,146 women; seven of these were borderline tumours, and eight were invasive.

Non-comparative Studies

Eleven prospective cohort studies (14-19,21-25) and one retrospective review (20) met the inclusion criteria for this evidence summary. The studies examine the yield, in terms of cancers detected, from various screening programs. The programs used serum CA 125, transabdominal ultrasound, transvaginal ultrasound, CDI (used in conjunction with grey-scale ultrasonography to show the ovarian blood vessels and their pattern of blood flow), or a combination of these tests. Where two tests were used, they were conducted either concurrently or sequentially. In the case of sequential testing, the second test was administered only to women who had positive results on the first test. The NHS review (12,13) pooled data on the number of cases of ovarian cancer detected across studies, but other data were not pooled, because of variability in the thresholds used to define abnormal test results and the follow-up methods employed.

Concurrent CA 125 and Ultrasonography

Six prospective cohort studies (14-19) and one retrospective review (20) were found that used the CA 125 test and transvaginal ultrasonography for screening women with a family history ovarian or breast (Table 5).

Lafromboise et al (20) reviewed the charts of 311 high-risk women from a registry of women currently undergoing screening for ovarian cancer. Lafromboise et al defined 'high-risk' women as women with a family history of ovarian cancer or a positive BRCA test. Of the fifty-seven women who underwent surgery, twenty-eight had surgery prior to study entry, but unfortunately there are no details as to why these women underwent surgery (prophylaxis versus pathology). Another twenty of the 57 women chose to undergo prophylactic oophorectomy. The remaining nine women underwent surgery because of abnormal test results (two abnormal CA 125s, six abnormal ultrasounds, and one abnormal CA 125 and ultrasound). One woman who had an abnormal ultrasound was found to have borderline ovarian cancer.

Tailor et al (19) prospectively studied 2,500 women who had at least one close relative with ovarian cancer. They found that 104 women had positive ultrasounds (4.1%), and they detected 11 cancers (seven stage I, four borderline). Tailor et al was the only study identified that did not report the number of women who underwent surgery due to abnormal test results.

Karlan et al (14) recruited 597 women with a family history of ovarian cancer to undergo screening via CA 125 analysis and ultrasound. Karlan et al studied patients with both transvaginal ultrasonography examinations and colour flow Doppler studies. They reported that 115 women had abnormal CA 125 or ultrasound findings. Of these women, 19 underwent surgery. Ten women underwent surgery because of consistently abnormal ultrasound findings, and 9 women underwent surgery because of genetic counselling or personal choice. One woman was found to have stage IA, borderline ovarian cancer. This woman had an abnormal ultrasound and a normal CA 125 test (14U/ml).

In the prospective study by Muto et al (15), 384 women with a family history of ovarian cancer underwent screening. Of these women, 38 (9.9%) underwent surgery. Ten women underwent surgery because of abnormal ultrasound results and five because of abnormal CA 125 levels. Nineteen women chose to undergo prophylactic oophorectomies. The remaining four women underwent surgery for other gynecologic indications. There were no cases of ovarian cancer detected during surgery.

Dorum et al (18) examined 180 women with a family history of ovarian cancer. Twenty-seven women underwent surgery. Thirteen women who had been treated for breast cancer previously had normal ultrasound findings but chose to undergo prophylactic oophorectomy. Two of those women were found to have ovarian cancer. Of fourteen women who underwent surgery due to abnormal ultrasound findings, seven were diagnosed with ovarian cancer.

Schwartz et al (16) screened 247 women with a family history of ovarian cancer. One woman with abnormal ultrasound results who underwent surgery did not have ovarian cancer. Belinson et al (17) screened 137 women with a family history of ovarian cancer, each woman via ultrasonography and CA 125. Five women had abnormal CA 125 results, and four women had abnormal ultrasound results. Two of those women underwent surgery. One woman who was diagnosed with ovarian cancer had a normal CA 125 test initially; however, after an abnormal ultrasound, her CA 125 level was measured again and revealed an elevated CA 125 level (42 U/ml).

Three studies that evaluated ultrasound and CA 125 reported follow-up data (18-20). That is, they followed the patients who were screened to identify if any additional cancers were detected years after screening. Dorum et al (18) detected no cancers among the women who returned for annual follow-up (56% follow-up rate). Tailor et al (19) reported that nine additional cancers were detected within the nine years after screening. All the cancers detected were at an advanced stage (stage III). Laframboise et al (20) followed the patients screened in their study for seven years. In that time, there was one case of stage I ovarian cancer detected among the screened women.

Positive predictive values calculated for each of the studies varied from 0% to 50%. This result suggests that between 0% and 50% of women who undergo surgery due to abnormal CA 125 and ultrasound results have ovarian cancer.

Table 5. Studies of concurrent CA 125 and ultrasonography (13).

Study	Karlan, 1993 (14)	Muto, 1993 (15)	Schwartz, 1995 (16)	Belinson, 1995 (17) [a]	Dorum, 1996 (18)	Laframboise, 2002 (20)	Tailor, 2003 (19)
Population	• age >35 • family history of OC, breast cancer	• age >25 • family history of OC	• age >30 • family history of OC	• age >25 • family history of OC	• age >18 • 2 FDR with breast or OC, or 1 with breast and OC	• 2 FDR with OC • 2 FDR with breast and 1 with OC • 1 FDR with OC with Ashkenazi Jewish, French-Canadian or Dutch ancestry • 1 FDR with OC and 1 male FDR with breast cancer • 1 FDR with OC and 2 FDR with early onset breast, pancreatic or prostate cancer • any relative with known mutation	• 1 FDR with ovarian cancer [b]
CA 125 cut-off for repeat screening	>35 U/ml	≥35 U/ml	>35 U/ml	>35 U/ml	>35 U/ml	>35 U/ml	not reported
# participants	597	384	247	137	180	311	2,500
# undergoing surgery (%)	19 (3.2%)	38 (9.9%)	1 (0.4%)	2 (1.5%)	27 (15.0%)	57 (18.3%)	not reported
# undergoing surgery due to abnormal test results (%)	10 (1.7%)	15 (3.9%)	1 (0.4%)	2 (1.5%)	14 (7.8%)	9 (2.9%)	not reported
# ovarian cancers detected [c]	1 (borderline)	0	0	1	7 (3 borderline)	1 (borderline)	11 (4 borderline)
# false-positives	9	15	1	1	7	8	93 [d]
Positive predictive value	10%	0%	0%	50%	50%	11%	10.5%

Note: CA 125, cancer antigen; FDR, first degree relative; OC, ovarian cancer.

[a] Colour Doppler imaging used in addition to transvaginal ultrasound and CA 125

[b] Inclusion criteria changed over time, eventually, women included in the study had to have one first degree relative with ovarian cancer, and at least one other relative with first or second degree with any cancer.

[c] Number of ovarian cancers detected among women who underwent surgery for abnormal test results.

[d] False positive value is based on the number of abnormal screening tests, as opposed to the number of surgery performed that did not identify malignant disease.

Sequential CA 125 and Ultrasonography

Two prospective cohort studies examined sequential CA 125 and ultrasonography (21,22) (Table 6). The prospective study by Taylor et al (22) is the most recent study using sequential CA 125 and ultrasound in women at high risk for ovarian cancer. Neither study tested consistently for BRCA mutations; women were enrolled in the study based on a family history of ovarian cancer.

The prospective cohort study by Taylor et al (22) screened high-risk women using CA 125 followed by ultrasonography, if the CA 125 value was greater than 20 U/ml in premenopausal women and greater than 6 U/ml in postmenopausal women. The majority of women in the study were premenopausal (210 of 258). Twenty-four women underwent surgery, but Taylor et al reported that only three of these surgeries were "initiated" by the study. Whether the remaining 21 women who underwent surgery chose to do so for prophylaxis or for another reason is unclear. None of the three women who underwent surgery "initiated" by the study were found to have ovarian cancer. However, two women were found to have advanced stage ovarian cancer among the women who were undergoing surgery for other reasons.

Bourne et al (21) screened 1,601 women with CA 125, transvaginal ultrasound, and CDI. Eighty-eight percent of the women in the study had at least one first-degree relative with ovarian cancer. At the time of the ultrasound a blood sample was also taken. Of sixty-two women who underwent surgery due to abnormal ultrasound results, seven were found to have ovarian cancer, including three women with borderline tumours. At diagnosis, the blood samples taken at the time of the ultrasound were examined. Three of the seven women diagnosed with ovarian cancer had elevated CA 125 levels (>35U/ml).

The PPV for the sequential CA 125 and ultrasonography ranged from 0% to 11.2%. In Taylor et al's study, the PPV suggests that surgery will detect zero cancers. It is important to recognize that the small incidence of ovarian cancer means that studies, including PPV, need to have large sample sizes in order to achieve accurate results.

Table 6. Studies of sequential CA 125 and ultrasonography.

Study	Bourne, 1994 (21)	Taylor, 2001 (22)
Population	• age >25 • family history of ovarian cancer	• age >35 • family history of ovarian cancer
CA 125 cut-off for repeat screening	varied (10-35 U/ml)	>20 U/ml (premenopausal) >6 U/ml (postmenopausal)
# participants	1601	252
# undergoing surgery (%)	62 (4.1%)	24 (9.5%)
# undergoing surgery because of abnormal test result	62 (4.1%)	3 (1.2%) [a]
# ovarian cancers detected	7 (3 borderline)	0
# false-positives	55	3
Positive predictive value	11.2%	0%

[a] Taylor et al reported that 3 surgeries were 'initiated' by the study. It is not clear whether the other women undergoing surgery chose prophylactic surgery or not.

Ultrasonography Plus Colour Doppler Imaging

One prospective cohort study reported the results of transvaginal ultrasonagraphy and CDI screening in high-risk women (23) (Table 7). Weiner et al (23) screened 600 women with previous breast cancer with concurrent ultrasound and CDI. Sixty-four women had abnormal ultrasound results. Twelve of those women underwent surgery. Among the 12, there were three women with non-metastatic malignant ovarian cancer and one woman with metastatic ovarian cancer. This study had the highest PPV of all the studies included in this evidence

summary--33.3%--which means that of the women who underwent surgery due to abnormal ultrasound and CDI results, one third had ovarian cancer (true positives).

Table 7. Study of ultrasonography and CDI (13).

Study	**Weiner, 1993 (23)**
Population	previous breast cancer
Screening program	concurrent ultrasound and CDI
# participants	600 women with previous breast cancer
# undergoing surgery (%)	12 (2.0%)
# undergoing surgery due to abnormal results (%)	12 (2.0%)
# ovarian cancers detected	4 (1 metastatic)
# false-positives	8
Positive predictive value	33.3%

Ultrasonography alone

Two prospective cohort studies were found that evaluated screening using ultrasound alone (24,25) (Table 8). Andolf et al (24) offered screening to all women in the target age group (40 to 70) who contacted the gynecology clinic for any reason, but did not report either the number with a family history of ovarian cancer or the proportion of women attending the clinic because of symptoms (24). They screened 805 women for ovarian cancer. Eighty-three of those women had initial abnormal ultrasound scans, and upon repeat scanning, 50 had abnormal results. Thirty-nine of the 50 women underwent surgery. Two women were diagnosed with borderline ovarian tumours, and one woman was diagnosed with stage III ovarian cancer.

Van Nagell et al (25) included two groups of women: 1) those 50 years of age or older and 2) those age 25 or more with a family history of ovarian cancer. The number of women undergoing surgery was not reported separately for those two groups. Two hundred and fifteen women who had normal ultrasound results chose to undergo surgery, and 180 women underwent surgery because of abnormal ultrasound results. Seventeen of the 180 women who underwent surgery because of abnormal ultrasound results were diagnosed with ovarian cancer. Eleven women had stage I disease, three women had stage II, and three women had stage III disease. No cases of ovarian cancer were detected among the 215 women who chose to undergo surgery. Van Nagell et al reported a PPV of 9.4%,suggesting that 9.4% of women who undergo surgery because of abnormal ultrasound results alone will have ovarian cancer, while more than 90% of women with abnormal ultrasounds will undergo unnecessary surgery.

Table 8. Studies ultrasonography alone (13).

Study	**Andolf, 1986 (24)**	**van Nagell, 2000 (25)**
Population	age 40-70	Women ≥25, with a family history of OC OR women ≥50 (regardless of history)
# participants	805	14,469
type of ultrasound	transabdominal	transvaginal
# undergoing surgery (%)	39 (4.8%)	395 (2.7%)
# undergoing surgery due to abnormal results (%)	39 (4.8%)	180 (1.2%)
# ovarian cancers detected	3 (2 borderline)	17 (11 stage I; 3 stage II; 3 stage III)
# false-positives	36	163
Positive predictive value	7.7%	9.4%
Cancers arising during follow-up (duration of follow-up)	not reported	4 within 12 months 4 after 12 months

Note: OC, ovarian cancer

Frequency of Screening

No evidence emerged on the effects of different screening intervals on detection rates for ovarian cancer (13).

Adverse Psychological Effects

The NHS review (13) found a qualitative evaluation of the psychological effects of a false-positive diagnosis for ovarian cancer in women with a family history of ovarian cancer (26). Pernet et al (26) administered questionnaires designed to measure psychological distress, anxiety, and depression to 15 women before and three months after surgery that was performed because of abnormal screening ultrasound scans. The women waited between three weeks and five months for surgery. None of the women were found to have ovarian cancer. Ten participants were interviewed 12 to 21 months after surgery. The NHS reviewers concluded that the women interviewed were "not severely distressed" about their experience. Anxiety levels were highest in the time interval between surgery and biopsy results becoming available to the patient, which was four weeks in one case and 18 months in another.

There have been two observational studies published that have surveyed women regarding their perceived risk of developing ovarian cancer (27,28). Andersen et al (27) reported results for 3,257 women who responded to a mailed survey. They found that women with one relative with ovarian cancer had a higher perceived risk of developing cancer than their true risk. They also noted that women with two or more relatives with ovarian cancer had a lower perceived risk of developing ovarian cancer than their true risk.

Cull et al (28) administered a questionnaire to 196 women in a familial ovarian cancer clinic. The questionnaire included the General Health Questionnaire (GHQ-30), which measures psychological distress and dysfunction. Thirty percent of the women who completed the questionnaire obtained scores that would suggest that they were highly distressed. Cull et al's multiple regression indicated that well-educated (university graduates), anxiety-prone women were more likely to present with high levels of distress regarding their cancer risk. Similar to Andersen et al's findings, Cull et al (28) noted that women with a family history of ovarian and breast cancer seemed to underestimate their risk of developing ovarian cancer.

V. INTERPRETIVE SUMMARY

The evidence available on screening high-risk women for ovarian cancer is limited. Cohort studies provide data on the PPV of screening but little on the sensitivity of screening tests in this setting. The screening tests evaluated have low PPVs, resulting in 12% of healthy women being recalled for further testing and assessment (13). The proportion of women without evident cancer who had investigational surgery following screening with ultrasound alone appeared to be higher (1.0% to 4.9%). No evidence is available about the appropriate interval for screening.

Ultrasonography and CA 125 can detect early ovarian cancer. Fifty percent of the cancers detected with ultrasound-based screening (95% CI, 34% to 78%) were stage I. Preliminary evidence from a randomized trial suggests that, in the general population, this may translate into longer survival for women whose cancers are detected by screening (29), but similar trials have not been conducted in high-risk groups.

The data available from the NHS review (13) suggest that ovarian cancer will be found in five of every 1,000 women with a family history of ovarian cancer who participate in an ultrasound-based screening program. Sixty percent of those cancers will be early-stage disease. Estimates vary widely for the number of women who will undergo surgery as a result of a positive screening test but will be found not to have ovarian cancer; false-positive rates of 0.4 to 4.9% have been reported with 96% confidence intervals up to 14%.

VI. ONGOING TRIALS

The Physician Data Query (PDQ) database of clinical trials on the Internet (http://www.cancer.gov/search/clinical_trials/ searched January 25, 2004) were searched for reports of ongoing trials.

There are no ongoing randomized trials involving women with a family history of ovarian cancer, but the United Kingdom Committee for Coordinating Cancer Research (UKCCCR) is conducting a prospective uncontrolled screening study in this population, using CA 125 and transvaginal ultrasound (13). Survival results from three large ongoing randomized controlled trials of screening for ovarian cancer in women from the general population are not expected until midyear 2004.

VII. FUTURE RESEARCH

In addition to assessing the impact of screening on survival, future research needs to focus on the ideal sequencing of screening tests. More tumour markers need to be identified that detect ovarian cancer more accurately than does cancer antigen 125.

Some researchers are combining several tumour markers to attempt to increase accuracy (30-32). Crump et al (30) characterized the behaviour of five tumour markers: CA 125, Herceptin (HER-2/*neu*), urinary gonadotropin peptide (UGP), lipid-associated sialic acid (LASA), and Dianon marker 70/K (DM/70K). They determined that all the markers behaved independently of each other, which is clinically relevant, because they concluded that the combined false-positive rate from screening with multiple markers may be estimated by the individual false-positive rates (30). Woolas et al (31) screened 429 women with pelvic masses and concluded that combining multiple tumour markers increased both specificity and sensitivity. However, when Cane et al (32) specifically studied women at risk for ovarian cancer, they detected that combining tumour markers increased specificity but jeopardized sensitivity. More high quality studies need to examine the interaction between tumour markers and the sensitivity and specificity of each of these tumour markers.

Other researchers are attempting to define new markers to identify ovarian cancer. Mok et al (33) detected that prostasin, a molecular marker, is overexpressed in women with ovarian cancer. Further research is required to assess prostasin as a tumour marker for screening for ovarian cancer. Katsaros et al (34) reported in a published abstract that their analysis of human kallikrein 6 (hK6) and 10 (hK10) concentrations in healthy women and women with ovarian carcinoma (34) detected elevated levels of the biomarkers in the women with ovarian carcinoma ($p < 0.001$). They concluded that hK6 and hK10 are new biomarkers for carcinoma that may improve the sensitivity and specificity of screening tests when combined with CA 125.

Longitudinal screening algorithms using these novel tumour markers also need to be developed because CA 125 algorithms are computationally intensive (35). Petricoin et al (36) used proteomic pattern technology to attempt to define an algorithm to identify ovarian cancer. They identified a 'cluster pattern' that was able to distinguish all ovarian cancer cases from non-ovarian cancer cases, including 18 stage I cases. These findings are very promising and require more research to determine their accuracy in a clinical setting.

VIII. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Draft Opinions

Based on the evidence reviewed, the Gynecology Cancer DSG drafted the following opinions:

Target Population

This evidence summary applies to women who are at high risk for developing ovarian cancer (as defined by the American Society of Clinical Oncology, Appendix 1).

Draft Opinions

The lack of sufficient high quality evidence precludes definitive recommendations from being made. Instead, the Gynecology Cancer Disease Site Group offers the following opinions based on the evidence reviewed:

- the population of women who are at high risk for developing ovarian cancer has not been studied adequately enough to establish that screening is beneficial.
- More long-term studies of women who are at high risk for developing ovarian cancer need to be conducted in order to determine if there is any benefit from screening.
- Women may experience distress regarding their perceived risk of ovarian cancer regardless of their familial ovarian cancer risk. Practitioners should acknowledge this distress and educate women about their risk of developing ovarian cancer and the effectiveness of available screening tests.
- There are no high quality randomized controlled trials examining the role of screening women at high risk for developing ovarian cancer. Such trials would be of benefit to the gynecologic oncologists and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

Practitioner Feedback

The draft version of this report was reviewed by Ontario practitioners. Any changes made to the report as a result of practitioner feedback are described in the "Modifications" section below.

Methods

Practitioner feedback was obtained through a mailed survey of 71 practitioners in Ontario (40 medical oncologists, 16 surgeons, 14 gynecologists and 1 urologist). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on February 3, 2004. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology Cancer DSG reviewed the results of the survey.

Results

Thirty responses were received out of the 71 surveys sent (42.3% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, nineteen indicated that the report was relevant to their clinical practice and completed the survey. Results of the practitioner feedback survey are summarized in Table 9.

Table 9. Results of the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing an evidence summary, as stated in the "Choice of Topic" section of the report, is clear.	17 (89.5%)	2 (10.5%)	--
There is a need for an evidence summary on this topic.	16 (84.2%)	3 (15.8%)	--
The literature search is relevant and complete in this evidence summary.	15 (78.9%)	4 (21.1%)	--
I agree with the methodology used to summarize the evidence.	17 (89.5%)	2 (10.5%)	--
I agree with the overall interpretation of the evidence in the evidence summary.	17 (89.5%)	1 (5.3%)	1 (5.3%)
The "Opinions of the Disease Site Group" section of this evidence summary is useful.	16 (84.2%)	1 (5.3%)	2 (10.5%)
An evidence summary of this type will be useful for clinical decision making.	15 (78.9%)	2 (10.5%)	2 (10.5%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	14 (73.7%)	3 (15.8%)	2 (10.5%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	14 (73.7%)	4 (21.1%)	1 (5.3%)

Summary of Written Comments

Three of the respondents (16%) provided written comments:

1. If someone has a high risk of developing cancer, they require close follow-up or prophylactic surgery.
2. As there is no evidence at present that screening high-risk women is beneficial, this document should state that at this time screening is not recommended.
3. More emphasis should be put on the need to determine what a woman's risk is.

Modifications/Actions

1. The Gynecology Cancer DSG agreed that if a woman is at high risk for developing ovarian cancer, she should consider prophylactic surgery. The purpose of this evidence summary was to review the evidence regarding screening; however, the Gynecology Cancer DSG's evidence summary 4-4 entitled *Management Options for Women with a Hereditary Predisposition to Ovarian Cancer* describes the evidence surrounding prophylactic oophorectomy (http://www.cancercare.on.ca/pdf/pebces4-4f.pdf).
2. The Gynecology Cancer DSG stated in the "Opinions of the Gynecology DSG" section that "the population of women who are at high risk for developing ovarian cancer has not been studied adequately enough to establish that screening is beneficial". The purpose of an evidence summary is to present the available evidence, even though there is not enough evidence to make recommendations. The Gynecology Cancer DSG does not believe there is sufficient evidence at this time to recommend for or against screening a high-risk population for ovarian cancer.
3. The Gynecology Cancer DSG agreed that the evidence summary had to be clear about its definition of high risk. The table of the ASCO definition of ovarian cancer risk was moved from the Appendix to the "Choice of Topic and Rationale" section, so that it is right up front. Also, more detail was added to the text in the "Choice of Topic and Rationale" regarding the definition of high risk.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to members of the PGCC for review and approval. Nine of 15 members of the PGCC returned ballots. Six PGCC members approved the evidence summary report as written, and one member approved the report with minor modifications required. Two members approved the report conditional on the Gynecology DSG addressing their comments. Referring to the second bullet of the key evidence, one PGCC member felt that the median is not a clinically useful way of summarizing the PPV. Using the median suggests that in half the studies the PPV was higher and in half the studies it was lower. The other PCGG member commented that the first bullet in the "Opinions" section was a passive statement and suggested a more appropriate phrasing for the statement.

Modifications/Actions

Upon review of the "Key Evidence" section, the Gynecology Cancer DSG decided to add an additional three bullets to further describe the evidence. The bullet regarding PPV was revised to add the range of PPV across the studies, as opposed to the median. The bullet in the "Opinions" section was modified as per the suggestion of the PGCC member.

IX. OPINIONS OF THE GYNECOLOGY CANCER DISEASE SITE GROUP

The lack of sufficient high-quality evidence precludes definitive recommendations being made. Instead, the Gynecology Cancer DSG offers the following opinions, based on the evidence reviewed:

- Studies are inadequate to establish benefits from screening the population of women who are at risk for developing ovarian cancer.
- The population of women who are at high risk for developing ovarian cancer has not been studied adequately enough to establish that screening is beneficial.
- More long-term studies of women who are at high risk for developing ovarian cancer need to be conducted in order to determine if there is any benefit from screening.
- Women may experience distress about their perceived risk of ovarian cancer regardless of their familial ovarian cancer risk. Practitioners should acknowledge this distress and educate women about their risk of developing ovarian cancer and the effectiveness of available screening tests.
- There are no high-quality randomized controlled trials examining the role of screening women at high risk for developing ovarian cancer. Such trials would be of benefit to health care providers and the patients they serve. Patients and practitioners should be encouraged to take part in such trials.

X. JOURNAL REFERENCE

Manuscript development in progress.

XI. ACKNOWLEDGMENTS

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For a complete list of the Gynecology Cancer Disease Site Group members and the Practice Guidelines Coordinating Committee members, please visit the CCO website at: http://www.cancercare.on.ca/.

REFERENCES

1. National Cancer Institute of Canada and Canadian Cancer Statistics 2002. Geographic patterns of cancer occurrence. 2002.
2. Lynch HT, Albano W, Black L, Lynch JF, Recabaren J, Pierson R. Familial excess of cancer of the ovary and other anatomic sites. *JAMA* 1981;245:261-4.
3. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117-30.
4. Berchuck A, Schildkraut JM, Marks JR, Futreal PA. Managing hereditary ovarian cancer risk. *Cancer* 1999;86:2517-24.
5. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, et al. Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* 2001;68:700-10.
6. Andersen MR, Peacock S, Nelson J, Wilson S, McIntosh M, Drescher C, et al. Worry about ovarian cancer risk and use of ovarian cancer screening by women at risk for ovarian cancer. *Gynecol Oncol* 2002;85:3-8.
7. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H, et al. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med* 1998;339:424-8.
8. Narod SA, Sun P, Ghadirian P, Lynch H, Isaacs C, Garber J, et al. Tubal ligation and risk of ovarian cancer in carriers of BRCA1 or BRCA2 mutations: a case-control study. *Lancet* 2001;357:1467-70.
9. Browman GP, Levine MN, Mohide EA, Hayward RS, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502-12.
10. American College of Physicians. Screening for ovarian cancer: recommendations and rationale. *Ann Intern Med* 1994;121:141-2.
11. Guide to clinical preventive services. 2nd ed. Baltimore: Williams & Wilkins; 1996. p.159.
12. Bell R, Petticrew M, Sheldon T. The performance of screening tests for ovarian cancer: results of a systematic review. *Br J Obstet Gynaecol* 1998;105:1136-47.
13. Bell R, Petticrew M, Luengo S, Sheldon TA. Screening for ovarian cancer: a systematic review. *Health Technol Assess (Winchester, England)* 1998;2:i-iv.
14. Karlan BY, Raffel LJ, Crvenkovic G, Smrt C, Chen MD, Lopez E, et al. A multidisciplinary approach to the early detection of ovarian carcinoma: rationale, protocol design, and early results. *Am J Obstet Gynecol* 1993;169:494-501.
15. Muto MG, Cramer DW, Brown DL, Welch WR, Harlow BL, Xu H, et al. Screening for ovarian cancer: the preliminary experience of a familial ovarian cancer center. *Gynecol Oncol* 1993;51:12-20.
16. Schwartz PE, Chambers JT, Taylor KJ. Early detection and screening for ovarian cancer. *J Cell Biochem* 1995;23(Suppl):233-7.
17. Belinson JL, Okin C, Casey G, Ayoub A, Klein R, Hart WR, et al. The familial ovarian cancer registry: progress report. *Cleve Clin J Med* 1995;62:129-34.
18. Dorum A, Kristensen GB, Abeler VM, Trope CG, Moller P. Early detection of familial ovarian cancer. *Eur J Cancer* 1996;32A:1645-51.
19. Tailor A, Bourne TH, Campbell S, Okokon E, Dew T, Collins WP. Results from an ultrasound-based familial ovarian cancer screening clinic: a 10-year observational study. *Ultrasound Obstet Gynecol* 2003;21:378-85.

20. Laframboise S, Nedelcu R, Murphy J, Cole DEC, Rosen B. Use of CA-125 and ultrasound in high-risk women. *Int J Gynecol Cancer* 2002;12:86-91.
21. Bourne TH, Campbell S, Reynolds K, Hampson J, Bhatt L, Crayford TJB, et al. The potential role of serum CA 125 in an ultrasound-based screening program for familial ovarian cancer. *Gynecol Oncol* 1994;52:379-85.
22. Taylor KJ, Schwartz PE. Cancer screening in a high risk population: a clinical trial. *Ultrasound in Med & Biol* 2001;27:461-6.
23. Weiner Z, Beck D, Shteiner M, Borovik R, Ben-Shachar M, Robinzon E, et al. Screening for ovarian cancer in women with breast cancer with transvaginal sonography and color flow imaging. *J Ultrasound Med* 1993;12:387-93.
24. Andolf E, Svalenius E, Astedt B. Ultrasonography for early detection of ovarian carcinoma. *Br J Obstet Gynaecol* 1986;93:1286-9.
25. van NJ, Jr., DePriest PD, Reedy MB, Gallion HH, Ueland FR, Pavlik EJ, et al. The efficacy of transvaginal sonographic screening in asymptomatic women at risk for ovarian cancer. *Gynecol Oncol* 2000;77:350-6.
26. Pernet AL, Wardle J, Bourne TH, Whitehead MI, Campbell S, Collins WP. A qualitative evaluation of the experience of surgery after false positive results in screening for familial ovarian cancer. *Psycho Oncol* 1992;1:217-33.
27. Andersen MR, Peacock S, Nelson J, Wilson S, McIntosh M, Drescher C, et al. Worry about ovarian cancer risk and use of ovarian cancer screening by women at risk for ovarian cancer. *Gynecol Oncol* 2002;85:3-8.
28. Cull A, Fry A, Rush R, Steel CM. Cancer risk perceptions and distress among women attending a familial ovarian cancer clinic. *Br J Cancer* 2001;84:594-9.
29. Jacobs IJ, Skates SJ, MacDonald ND, Menon U, Rosenthal AN, Davies AP, et al. Screening for ovarian cancer: a pilot randomised controlled trial. *Lancet* 1999;353:1207-10.
30. Crump C, McIntosh MW, Urban N, Anderson G, Karlan BY. Ovarian cancer tumor marker behavior in asymptomatic healthy women: Implications for screening. *Cancer Epidemiol Biomarker Prev* 2000;9:1107-11.
31. Woolas RP, Conaway MR, Fengji X, Jacobs IJ, Yu YH, Daly L, et al. Combinations of multiple serum markers are superior to individual assays for discriminating malignant from benign pelvic masses. *Gynecol Oncol* 1995;59:111-6.
32. Cane P, Azen C, Lopez E, Platt LD, Karlan BY. Tumor marker trends in asymptomatic women at risk for ovarian cancer: Relevance for ovarian cancer screening. *Gynecol Oncol* 1995;57:240-5.
33. Mok SC, Chao J, Skates S, Wong K, Yiu GK, Muto MG, et al. Prostasin, a potential serum marker for ovarian cancer: identification through microarray technology. *J Natl Cancer Inst* 2001;93:1458-64.
34. Katsaros D, Fracchioli S, Yousef GM, Luo LY, Scorilas A, Puopolo M, et al. Human kallikrein 6 (hK6) and 10 (hK10): New potential serum biomarkers for diagnosis and prognosis of epithelial ovarian cancer [abstract]. *Proc Ann Meeting Am Soc Clin Oncol* 2002: 20
35. McIntosh MW, Urban N, Karlan BY. Generating longitudinal screening algorithms using novel biomarkers for disease. *Cancer Epidemiol Biomarker Prev* 2002;11:159-66.
36. Petricoin EF, Ardekani AM, Hitt BA, Levine PJ, Fusaro VA, Steinberg SM, et al. Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002;359:572-7.

Appendix 1. Causes of elevated CA 125.

Rosenthal & Jacobs[1] list several conditions other than ovarian cancer that may be associated with an elevated CA 125 result. These conditions include:

- other gynecologic conditions (endometriosis, fibroids, hemorrhagic ovarian cysts, menstruation, acute pelvic inflammatory disease, pregnancy)
- gastrointestinal or hepatic conditions (acute pancreatitis, colitis, chromic active hepatitis, cirrhosis, diverticulitis)
- other malignancies (bladder, breast, endometrial, lung, liver, non-Hodgkin's lymphoma, pancreatic)
- miscellaneous (pericarditis, polyarteritis nodosa, renal disease, Sjogren's syndrome, systemic lupus erythematosus).

[1] Rosenthal AN, Jacobs IJ. The role of CA 125 in screening for ovarian cancer. *Int J Biol Markers* 1998;13:216-20.

Appendix 2. Staging of ovarian cancer—International Federation of Obstetrics and Gynecology (FIGO).

Stage I Growth limited to the ovaries

Ia Growth limited to one ovary; no ascites present containing malignant cells. No

Ib Growth limited to both ovaries; no ascites present containing malignant cells. No tumour on the external surfaces; capsules intact

Ic Tumour either Stage Ia or Ib, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings

Stage II Growth involving one or both ovaries with pelvic extension

IIa Extension and/or metastases to the uterus and/or tubes

IIb Extension to other pelvic tissues

IIc Tumour either Stage IIa or IIb, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings

Stage III Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal Stage III. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum

IIIa Tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologic-proven extension to small bowel or mesentery

IIIb Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative

IIIc Peritoneal metastasis beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes

Stage IV Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV