Evidence Summary Report 4-6a EDUCATION AND INFORMATION 2014

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

Screening Postmenopausal Women for Ovarian Cancer

M. Fung Kee Fung, P. Bryson, M. Johnston, A. Chambers,
and the members of the Gynecology Cancer Disease Site Group

Report Date: January 2004

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Screening Postmenopausal Women for Ovarian Cancer
Evidence Summary Report # 4-6a- EDUCATION AND INFORMATION 2014

M. Fung Kee Fung, P. Bryson, M. Johnston, A. Chambers, and the members of the Gynecology Cancer Disease Site Group

ORIGINAL EVIDENCE SUMMARY: March 17, 2003
MOST RECENT LITERATURE SEARCH: January 2004
NEW EVIDENCE ADDED TO EVIDENCE SUMMARY: January 2004

In August 2004 a systematic review of the evidence presented in this evidence summary was published in the *Journal of Obstetrics and Gynaecology Canada*:
Fung Kee Fung M, Bryson P, Johnston M, Chambers A. Screening postmenopausal women for ovarian cancer: A systematic review. J Obstet Gynaecol Can. 2004;26:717-28.

SUMMARY

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.

Question

Is there a role in Ontario for screening asymptomatic postmenopausal women in the general population for ovarian cancer? Outcomes of interest were the performance of screening tests assessed in terms of predictive values, sensitivity and specificity, the stage of screen-detected disease at diagnosis, and survival.

Target Population

This evidence summary applies to the general population of postmenopausal women who are not at increased risk for ovarian cancer (e.g., women who do not have of a positive family history of disease).

Methods

Entries to MEDLINE (1966 through January 2004), CANCERLIT (1983 through October 2002), and Cochrane Library (2003, Issue 4) databases and abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology from 1997 to 2003 were systematically searched for evidence relevant to this evidence summary report.

Evidence was selected and reviewed by two members of the Cancer Care Ontario Practice Guidelines Initiative's Gynecology Cancer Disease Site Group and methodologists. This evidence-summary-in-progress 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 community representatives.

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

The Cancer Care Ontario 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

- Three pilot randomized controlled trials and 18 prospective cohort studies were identified that investigated screening for ovarian cancer among postmenopausal women.
- Three randomized controlled trials that are evaluating the effects of screening are currently underway.
- Cancer antigen 125 and ultrasounds were the primary screening tests evaluated.
- Ultrasound and cancer antigen 125 have low positive predictive values, resulting in 12% of healthy women being recalled for more testing, and a false positive rate of 0.1% to 0.6%.
- The results from a randomized controlled trial led to the conclusion that of every 10,000 women participating in an annual screening program with cancer antigen 125 for three years:
  - 800 (8%) will have an ultrasound scan because of an elevated cancer antigen 125,
  - 30 (.3%) will undergo a surgical investigation because of an abnormal ultrasound,
  - 6 (.06%) will have ovarian cancer detected at surgery (approximately half of these will be early-stage disease and stand a chance of cure)
  - 24 (.24%) undergoing surgery will be found not to have ovarian cancer,
  - 10 (.1%) will have ovarian cancer detected over the next eight years.
- Currently, there is no screening strategy available for ovarian cancer in women in the general population.
- In addition, there is a lack of evidence to justify a population-screening tool for ovarian cancer.

Opinions of the Gynecology Cancer Disease Site Group

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:

- There is insufficient evidence currently to support the introduction of screening in the asymptomatic, general-risk, postmenopausal population.
- Screening is associated with increased rates of surgery and patient anxiety.
- The benefits of screening in terms of lives saved, pain, and suffering do not appear to be outweighed by the social costs of unnecessary investigations and treatments.
- Detection of early-stage cancers may not lead to increased survival rates.
- No optimal interval for screening can be defined.
- The positive predictive value of the screening tests needs to be improved.
- Any further recommendations regarding screening for ovarian cancer in this group of women must await the conclusions of the three major ongoing trials.
- Efforts to impact ovarian cancer-related mortality rates should in the meantime focus on prevention, including:

a) Identifying women at high risk followed by genetic counselling and BRCA1 and BRCA2 identification (Appendix 2). The use of prophylactic oophorectomy in identified BRCA1 or 2 carriers needs to be further explored.
b) Making available to both patients and health care providers information about the benefits of oral contraceptive use and tubal ligation in prevention.

Related Evidence Summaries
Practice Guidelines Initiative's Evidence Summary Reports:

- #4-4 *Management Options for Women with a Hereditary Predisposition to Ovarian Cancer*
- #4-6b *Screening High-Risk Women for Ovarian Cancer (in progress)*

For further information about this evidence-summary-in-progress 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/access_PEBC.htm
for all additional Practice Guidelines Initiative reports.

PREAMBLE: About Our Evidence-Summary-in-Progress Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario 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.

In the current step of the cycle, the evidence-summary-in-progress report has been sent to practitioners across Ontario for feedback. The Disease Site Group will review this feedback and modify the evidence summary report where necessary. The resulting evidence summary report will then be submitted to the Practice Guidelines Coordinating Committee for formal approval.

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.

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Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

FULL REPORT- ARCHIVED 2014

I. QUESTION

Is there a role in Ontario for screening asymptomatic postmenopausal women in the general population for ovarian cancer? Outcomes of interest were 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

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 gynaecologic cancer mortality (1). The lifetime risk of developing ovarian cancer is 1 in 70, or 1 in 2500 per year, in women over age 40 in the general population (2).

Seventy percent of ovarian cancers present as advanced disease (stages III and IV), which is associated with an overall five-year survival rate of 30% (3). Women with stage I disease represent 15% to 25% of cases with a five-year survival of 80% to 90% (4). Approximately 10% to 15% of patients have stage II disease with a five-year survival of 66% to 69% (4). Unfortunately, there is a lack of specific symptoms with early stage disease. The natural history of how epithelial ovarian cancer develops is not known, but indirect evidence suggests the progression time may be as short as two years (5).

Ovarian cancer is not a single disease; instead it encompasses a cluster of cancers that arise from multiple cell types. The majority of malignant ovarian cancers arise from epithelial cells; however, some malignancies are classified as germ cell tumours or sex cord stromal tumours (6). In addition to the various cell types from which ovarian cancer can develop, there are also varying degrees of the disease. There is also subgroup of serous class tumours that are considered borderline tumours because they are more invasive than benign tumours but have lower malignant potential than invasive malignant tumours (6). For the purposes of this evidence summary, women screened for ovarian cancer and diagnosed with invasive epithelial ovarian cancer will be considered true positives, unless otherwise stated.

III. BACKGROUND

Principles of Screening

A) Definitions (Table 1)

- 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): proportion of women with a positive screening test who have confirmed ovarian cancer [true positives/(true positives + false positives)]
- Sensitivity: proportion of women with ovarian cancer found by screening [true positives/(true positives + false negatives)] i.e., the chance that a person with cancer has a positive test.

Table 1. Principles of screening.

Test Result	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

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

B) Requirements of an Effective Screening Test

Certain requirements must be met for a screening test to be deemed effective (World Health Organization [WHO] Criteria) (7). That is, to reduce mortality from the disease in question:

1) The condition should be an important health problem (significant prevalence and cause of mortality).
2) The natural history of the condition, including development from latent to declared disease, should be adequately understood.
3) There should be a recognizable latent or early symptomatic stage in which treatment improves outcome.
4) There should be a suitable test or examination that is acceptable to the population.
5) There should be efficacious treatment for patients with recognized disease.
6) Facilities for diagnosis and treatment should be available.
7) There should be an agreed policy on whom to treat.
8) The screening program must be cost effective.
9) The screening tests should have a high sensitivity to detect disease (low false negative rate), a high specificity (low false positive rate), and high positive and negative predictive values.

The WHO has identified the above requirements plus six criteria for evaluating screening programs: validity, reliability, yield, cost, acceptance, and follow-up services (7). Validity refers to how well a screening test detects ovarian cancer, and yield refers to the number of cases of ovarian cancer detected.

C) The Current Situation

Both cancer antigen 125 (CA125) and endovaginal ultrasound are being used in an ad hoc fashion in a number of clinical settings, including screening asymptomatic postmenopausal women. Screening tests are being used outside of clinical trials or organized screening programs in an attempt to detect early ovarian cancer. Using CA125 for screening is problematic because many conditions other than ovarian cancer may be associated with an elevated CA125 result, including: endometriosis, fibroids, acute pelvic inflammatory disease, pregnancy, colitis, cirrhosis, or other malignancies (e.g. bladder, breast, lung, liver) (8).

Several approaches in the development of a screening protocol for ovarian cancer have been evaluated:

- CA125 as the primary screening test, with ultrasonography used for further testing of women with abnormal CA125 tests,
- Ultrasonography used as the primary screening test, with CA125 (or other tumour markers) used for further testing of women with abnormal ultrasound results,
- Ultrasonography alone,
- Colour Doppler imaging, used either concurrently with ultrasonography or used to further assess patients with abnormal ultrasound results.

The presence of ovarian cancer is confirmed by oophorectomy, the 'gold standard' for establishing the presence or absence of ovarian cancer. As this surgical procedure can be performed only on women who have symptoms or test results associated with ovarian cancer, women who do not undergo surgery must be followed for a reasonable period of time after screening to determine whether they develop symptoms or abnormal test results. For this reason, it is difficult to determine accurately the numbers of false negatives and true negatives associated with a screening program for ovarian cancer.

The aim of this evidence summary regarding screening postmenopausal women for ovarian cancer is to raise awareness about the issues and limitations of ovarian cancer screening and to aid decision-making by clinicians, women and policy makers. As women become more aware and fearful of developing ovarian cancer (9), they are demanding more screening tests. As a result, physicians are employing CA125 and ultrasound more frequently, despite the lack of evidence supporting the use of these screening tests. The hope is that the dissemination of evidence about utilizing these tests in postmenopausal women for screening will lead to an understanding of the benefits and limitations of these screening tests for ovarian cancer.

IV. 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 (10). Evidence was selected and reviewed by two members of the PGI's Gynecology Cancer Disease Site Group (DSG) and methodologists. Members of the Gynecology Cancer DSG disclosed potential conflict-of-interest information.

The evidence summary report is a convenient and up-to-date source of the best available evidence on screening postmenopausal 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 was obtained through a mailed survey. Final approval of the evidence summary report was obtained from the Practice Guidelines Coordinating Committee.

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 (1966 through October 2002), CANCERLIT (1983 through October 2002), and the Cochrane Library (2002, Issue 4) 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 2002 meetings of the American Society of Clinical Oncology (ASCO) and the Physician Data Query (PDQ) database of clinical trials on the Internet (http://www.cancer.gov/search/clinical_trials/; searched October 8, 2002) were searched for reports of ongoing trials. MEDLINE, 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, screening, and mass screening (as an exploded MeSH term). Search terms related to study design, 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.

Update

The original literature search has been updated using MEDLINE (through January 2004), the Cochrane Library (2003 Issue 4) and the 2003 proceedings of the annual meeting of ASCO.

Inclusion Criteria

Articles, reported in either full paper or abstract form, were selected for inclusion in this evidence summary if they met all of the following criteria:

1. were clinical trials (randomized controlled trials, comparative cohort studies, or single-cohort studies), systematic reviews of clinical trials, or practice guidelines,
2. evaluated tests to detect ovarian cancer,
3. included asymptomatic women from the general population,
4. reported rates of confirmed ovarian cancer.

Exclusion Criteria

Studies that evaluated screening programs for women at increased risk for ovarian cancer (e.g., because of a positive family history), women with symptoms suggestive of ovarian cancer, or women undergoing immediate gynecologic surgery were excluded.

Synthesizing the Evidence

The studies identified were separated into four intervention categories: 1) CA125 followed by ultrasonography, 2) ultrasonography followed by CA125, 3) ultrasonography alone and 4) colour Doppler imaging. The studies were not pooled because: some studies included the same participant populations; studies used various definitions of ovarian cancer (e.g., some included borderline tumours) or were of various lengths (e.g., some studies included the results of three annual screenings; some included results of only one screening); and there was variability in the definitions of abnormal test results. 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).

V. RESULTS

Update

Two additional prospective studies, reporting outcomes for general risk women undergoing screening for ovarian cancer, were added to the evidence summary in light of the comments the Gynecology Cancer DSG received from peer review (11,12). One study reported the results for women undergoing screening via CA125 and then ultrasonography (11); the other study reported the results of screening using ultrasound alone (12). Further details of these studies are reported in the results below.

Literature Search Results

Practice guideline, task force, and consensus recommendations

Recommendations have been published by six guideline, task force, and consensus groups in the past decade regarding screening for ovarian cancer (13-18); none of the publications recommend screening for ovarian cancer in women without a family history of the disease.

In 1994, the Canadian Task Force on Preventive Health Care concluded that screening for ovarian cancer, either by abdominal examination, pelvic or transvaginal sonography, or CA125 levels should be excluded from the periodic health examination of asymptomatic postmenopausal women (13)

In 1994, the American College of Physicians published a clinical guideline on screening for ovarian cancer in the *Annals of Internal Medicine* (14). Based on a systematic review of the

literature (15), they concluded that screening with ultrasound scan or serum CA125 for women without a family history of ovarian cancer was not recommended.

In 1995, a National Institute of Health (NIH) Consensus conference on ovarian cancer screening concluded that "there is no evidence available yet that the current screening modalities of CA125 and transvaginal ultrasonography can be effectively used for widespread screening to reduce mortality from ovarian cancer nor that their use will result in decreased rather than increased morbidity and mortality" (16).

In 1996, the United States Preventive Task Force issued an evidence-based practice guideline stating, "Screening asymptomatic women for ovarian cancer with ultrasound, the measurement of serum tumour markers, or pelvic examination is not recommended." (17)

In 1997 the American College of Preventive Medicine concluded that "the evidence is insufficient at this time to recommend physical examination, ultrasonography, biochemical markers, or genetic screening for asymptomatic women for early detection of ovarian malignancy" and the "research has not convincingly detected that screening will reduce morbidity or mortality from ovarian cancer or improve the health status of women".(18)

Randomized trials and cohort studies

Three pilot randomized controlled trials (RCTs) (19-21) and 18 cohort studies (1,11,12,22-36) form the basis of evidence for this evidence summary (Table 2). Six ovarian cancer screening guidelines (13-18) were also identified that have been published in the past decade. None of the guidelines recommended screening for women without a family history of ovarian cancer.

In 1998, the National Health Service (NHS) Centre for Reviews and Dissemination at the University of York (United Kingdom) published a systematic review of screening for ovarian cancer (6). The York review evaluated the effectiveness of screening programs, test performance, and the potential impact of screening (6). They pooled the number of cases of ovarian cancer detected by screening but did not pool other data available, because of variability in the thresholds used to define abnormal test results. The York review concluded that the most effective screening method and interval is unknown, and that, in the absence of evidence from RCTs, the effectiveness of screening programs for the general population could not be determined.

Overall, the York review (6) determined that annual ultrasound-based screening of general populations detected 100% of ovarian cancers (sensitivity) and CA125-based screening detected between 73% to 100% of ovarian cancers (depending on the study). The authors of the York review warned that these estimates have wide confidence intervals (CI) because of the small numbers of events available for analysis. Eight ovarian cancers were detected among 15,824 women screened with ultrasound (alone, or followed or accompanied by other tests), and 14 were detected among 27,560 women screened with CA125 followed by ultrasound. False positive rates ranged from 0.1% to 2.5%, depending on the combination of tests used. Seventy-five percent (95% CI, 35% to 97%) of the ovarian cancers detected by ultrasound-based screening and 50% of those detected by CA125-based screening (95% CI, 23% to 77%) were diagnosed at stage I.

Data from individual screening studies in the general population are presented below, categorized by the type of screening program used (CA125 followed by ultrasound, ultrasound followed by CA125, ultrasound alone or colour Doppler imaging).

Table 2. Studies included in this evidence summary.

Screening method	Reference	Type of study	Number of patients
CA125 followed by ultrasonography	Jacobs, 1999 (21)[a]	Pilot RCT	21,935
	Adonakis, 1996 (24)	Prospective cohort	2,000
	Grover, 1995 (22)	Prospective cohort	2,550
	Jacobs, 1993 (23)[a]	Prospective cohort	22,000
	Einhorn, 1992 (11)[b]	Prospective cohort	5,550
Ultrasonography followed by CA125	Sato, 2000 (28)	Prospective cohort	51,550
	Vuento, 1997 (27)[c]	Prospective cohort	1,291
	Holbert, 1994 (1)	Prospective cohort	478
Ultrasonography alone	van Nagell, 2000 (35)	Prospective cohort	14,469
	Hayashi, 1999 (12)	Prospective cohort	23,451
	Tabor, 1994 (19)	Pilot RCT	950
	Campbell, 1989 (29)[d]	Prospective cohort	5,479
	Millo, 1989 (30)	Prospective cohort	500
Colour Doppler imaging	Vuento, 1995 (33)[c]	Prospective cohort	1,364
	Kurjak, 1994 (34)	Prospective cohort	5,013
	Parkes, 1994 (20)	Pilot RCT	2,953
Follow-up studies	Crayford, 2000 (32)[d]	Prospective cohort	5,479
	Einhorn, 2000 (26)[b]	Prospective cohort	5,550
	Menon, 2000 (25)[a]	Prospective cohort	741
	Jacobs, 1999 (21)[a]	Pilot RCT	21,935
	Jacobs, 1996 (36)[a]	Prospective cohort	19,464

Note: CA125, cancer antigen 125; RCT, randomized controlled trial;
[a] Participants included in the Jacobs et al studies (21,23,36) and the Menon et al study (25) are from the same population.
[b] Participants included in the Einhorn et al studies (11,26) are from the same population.
[c] Participants included in the Vuento et al studies (27,33) are from the same population.
[d] Participants included in the Campbell et al study (29) and the Crayford et al study (32) are from the same population.

CA125 followed by ultrasonography (Table 3)

One pilot RCT (21) and four cohort studies (11,22-24) assessed screening using CA125 followed by ultrasonography in postmenopausal women. The pilot RCT by Jacobs et al (21) was designed to address issues of feasibility and screening performance for a larger randomized study, which would utilize this approach in ovarian cancer screening. It was not designed to measure the impact of screening on mortality and had limited power to do so. Invitations were sent to 22,000 women who had participated in a previous study of screening for ovarian cancer (23). Women were randomly allocated to either annual screening for three years (n=10,997) or follow-up without screening (n=10,958). In the screened group, a central laboratory measured serum CA125. Women with CA125 measures of 30U/ml or more were offered ultrasonography. During the first year of the study (which started in 1989), transabdominal ultrasound was used; and subsequent scanning was done with transvaginal ultrasound. Women with abnormal ultrasound results underwent a repeat scan and were referred to a gynaecologist for surgical investigation. Participants were followed up in 1997 through a national registry with mailed questionnaires to determine mortality status and if invasive primary epithelial cancer of the ovary or fallopian tube had been diagnosed. Surgical and histopathologic details were ascertained from medical records.

Eighty-six percent of women in the screening group had at least one assessment, and 71% completed all three screens. Of 9,364 women screened, 781 (8.3%) had an ultrasound scan because of elevated CA125, and 3.7% (29 of 781) underwent surgical investigation. Six index cancers (invasive primary epithelial cancer of the ovary or fallopian tube) were detected at the time of surgical investigation, giving an overall positive predictive value for screening of

20.7% (6 of 29). Three tumours were stage I, and three were stage III. There were 23 false positives: 20 women did not have cancer at surgery (14 had benign ovarian tumours, four had fibroids and three had no abnormality) and three women had adenocarcinoma of unknown origin. There were no deaths or serious adverse events associated with surgery.

During the eight-year follow-up period, 30 additional women were found to have index cancers: 10 women in the screening group and 20 women in the control group. Thus, there were a total of 16 women with index cancers in the screened group and 20 in the control group. Ten percent of the index cancers detected in the control group and 31% of those in the screened group were stage I or II (p=0.171). The distribution of histologic type was similar in the two allocation groups, but more low- and moderate-grade tumours were detected in the screened group (11 of 16 versus 5 of 20 in the control group, p=0.024). Among women with an index cancer, median survival was 72.9 months in the screened group and 41.8 months in the control group (p=0.0112). Nine of 10,958 women allocated to screening and 18 of 10,977 allocated to control died from index cancers during the follow-up period (relative risk [RR] of death, 2.0; 95% CI, 0.78 to 5.13; p=0.083).

An important fact to acknowledge is that the 1999 study was designed as a pilot study, not a true randomized trial. The women involved in the study were included in another earlier study by Jacobs et al in 1993 (23), in which all 22,000 women underwent screening. Therefore, because even the women in the control group of the pilot RCT had undergone screening in the past, the 1999 study may not be a true representation of women in the general population. Also, participants in the study were volunteers and perhaps more motivated than the general population to seek screening. Jacobs et al, however, concluded that conducting a larger RCT to see if screening can reduce ovarian cancer mortality among postmenopausal women would be feasible.

In addition to the pilot RCT by Jacobs et al (21), four cohort studies also investigated CA125 followed by ultrasound as a possible screening strategy for postmenopausal women without a family history of ovarian cancer (11,22-24). One cohort study used the same patient population as the pilot RCT (23) and was the largest cohort study to date screening postmenopausal women for ovarian cancer. Jacobs et al included 22,000 women in their study, recruiting the women through newspaper advertisements and pamphlets in occupational health departments of companies. In total, there were 21 cases of ovarian or fallopian tube cancer (n=2) detected: 11 were detected through screening and eight were detected through follow-up, all within 22 months of screening. Of the 11 cases of ovarian cancer detected at screening, three were stage I, one was stage IIa, and seven cases were advanced stage (III or IV). Jacobs et al (23) did not indicate whether these women were experiencing any symptoms that may have led to a diagnosis regardless of screening.

Adonakis et al's prospective cohort study (24) screened 2,000 women with CA125 and pelvic examinations. They detected one invasive ovarian cancer, one borderline tumour, and one case of metastatic ovarian cancer (arising from the kidney). In their methods, Adonakis et al reported following patients for a year if they had normal CA125 levels; however, they did not provide results for this follow-up period. Einhorn et al (11) screened 5,550 women over the age of 40 with CA125. Of these women, 175 had elevated CA125 levels, 39 underwent surgery, and seven women were diagnosed with ovarian cancer. Of the 5,375 women with normal CA125 levels, six cases of ovarian cancer were identified (time point at diagnosis not specified). Grover et al's prospective cohort study (22) did not detect any cases of ovarian cancer among the 2,550 participants at the time of screening; however, 99 had elevated CA125 levels (>35U/ml). One case of ovarian cancer was detected 10 months after screening. At the time of screening, this woman had an elevated CA125 (43U/ml) and a normal vaginal examination and ultrasound.

Jacobs et al (23), Adonakis et al (24), and Einhorn et al (11) concluded that CA125 seemed to be an effective screening tool in the postmenopausal population; however, more

studies were required to confirm this effectiveness. Grover et al's (22) study was the only cohort study to conclude that CA125 was not an effective screening tool.

Table 3. Studies of CA125 followed by ultrasonography.

Study	Jacobs, 1999 (21)[a]	Adonakis, 1996 (24)	Grover, 1995 (22)	Jacobs, 1993 (23)[a]	Einhorn, 1992 (11)
Type of study	pilot RCT	cohort	cohort	cohort	cohort
Population	age ≥45, post	age ≥45, 65% post	age >40 or with family history (3%)	age ≥45, post	age ≥40
CA125 cut-off recall for U/S	≥30 U/ml	≥35 U/ml	>35 U/ml	≥30 U/ml	≥30 U/ml
# screenings	3 annual screens	1 screening	1 screening	1 screening	2 screenings
# participants	10958 screened (10977 control)	2,000	2,550	22,000	5,550
# elevated CA125	468	18	101	339	175
# positive screening U/S	29	18	16	41	NR
# undergoing surgery (%)	29 (0.3%)	14 (0.7%)	16 (0.6%)	41 (0.2%)	39 (0.7%)
# ovarian cancers detected	6 (ovarian or fallopian tube) 3 at 1st screen 3 at 3rd screen	3 (1 invasive ovarian, 1 borderline, 1 metastatic)	0	11 (3 stage I, 1 stage II, 7 stage III,IV)	7 (2 stage I, 2 stage II, 2 stage III, 1 not specified)
# false-positives	23	12	8	30	32
PPV	20.7%	14.3%	0	26.8%	15.4%
# cancers found in women with negative tests	NR	NR	NR	8 ovarian cancers (5 stage I, 3 stage III) within 6-22 months of screening	6 ovarian cancers (stage NR) within 3 years of screening
Cancers arising after 1 year	NR	0	1	3	1
Sensitivity after 1 year	NR	100%	NR	79%	NR

[a] Patients in both Jacobs et al studies (21,23) are from the same patient population.

Note: NR, not reported; post, post-menopausal; PPV, positive predictive value; RCT, randomized controlled trial; U/S, ultrasound

Ultrasonography followed by CA125 (Table 4)

Three cohort studies (1,27,28) measured transvaginal ultrasound followed by CA125 (Table 4). Vuento et al (33) screened 1,291 postmenopausal women for ovarian cancer with ultrasound. At the time of the ultrasound, a blood sample was also taken from the women. When the blood samples were analyzed three years later, 14 women had a CA125 level greater than 30 U/ml. All 14 women had normal ultrasound results. At the time of screening, one woman with an abnormal ultrasound was diagnosed with borderline ovarian malignancy. During the 3.5 year follow-up, another case of ovarian cancer was detected (stage Ia). In addition to the ovarian cancers, six other malignancies were detected through screening or follow-up. The eight women diagnosed with malignancy had CA125 levels ranging from 2.5U/ml to 30.9U/ml. Vuento et al concluded that CA125 levels added no benefit to the ultrasound results.

The other two cohort studies investigating ultrasound followed by CA125 levels reported that the combination was an effective screening program (1,28). However, it is important to note that the study by Holbert et al (1) only included 478 women, too small a sample size from which to draw any conclusions. The study by Sato et al (28) screened 51,550 women who had never been screened before. All women were over 30 years old; thus almost half of the women

were premenopausal (24,950). There were 16 cases of ovarian cancer (four borderline tumours) detected at screening and eight additional cases detected at follow-up. All 24 cases of ovarian cancer were detected in women ≥43 years old. Sato et al concluded that ultrasound and then CA125 is an effective screening program: 77% of the cases of ovarian cancer detected were stage I, potentially increasing survival for these women through early detection. However, there were 298 false positives (i.e., 298 women underwent surgery and did not have cancer detected). The PPV was only 6.9%.

Table 4. Studies of ultrasonography followed by CA125.

Study	Sato, 2000 (28)	Vuento, 1997 (27)	Holbert, 1994 (1)
Type of study	cohort	cohort	cohort
Population	age >30, 52% were postmenopausal	postmenopausal	postmenopausal
CA125 cut-off	NR	>30U/ml	>35U/ml
# participants	51,550	1291	478
# screenings	annually 10 years	1 screening	1 screening[a]
# positive screening U/S	4452	NR	33
# positive screening CA125 tests	2554 [b]	14	29
# undergoing surgery (%)	320 (0.6%)	NR	11 (2.3%)
# ovarian cancers detected	22 (4 borderline, 13 stage I, 2 stage II, 3 stage III-IV)	1 (borderline)	1 (stage I)
# false-positives	298	NR	10
Positive predictive value	6.9%	NR	9.1%
# cancers developing among women with negative screening tests	4 stage I ovarian cancers time frame not reported	4 cases: 1 stage I ovarian, 2 stage I endometrial, 1 abdominal carcinomatosis within 2 years of screening	NR

Note: NR, not reported; U/S, ultrasound.
[a] 32 women underwent two annual screenings because they enrolled early into the two year study.
[b] These women underwent further examination to attempt to explain abnormal test results, thus substantially fewer women actually underwent surgery.

Ultrasonography alone (Table 5)

There have been four cohort studies (12,29,30,35) and one pilot RCT (19) that have investigated ultrasonography alone in screening for ovarian cancer in the general population. The pilot RCT by Tabor et al (19) randomized 950 women to receive either screening with ultrasound or no screening. Tabor et al did not provide any baseline data on the control group, nor did they report that the women in the control group were followed up at any time to record their health status. Of the 435 women in the screening group, 29% were premenopausal. Tabor et al reported that 54 women had abnormal ultrasounds and that nine of these women underwent surgery; there were no cases of ovarian cancer identified.

The largest cohort study to date on using ultrasound alone to screen women in the general population (N=23,451) for ovarian cancer was published by Hayashi et al (12). Women were screened for ovarian cancer with transvaginal ultrasound at their annual uterine cervical screening. Ninety-five women underwent surgery because of repeatedly abnormal ultrasounds. Of these 95 women, seven cases of ovarian cancer were detected. The PPV for this study was 7.4%.

Van Nagell et al (35) have also published results of a large cohort of 14,469 women who underwent annual screening from 1987 to 1999. They detected 17 cases of ovarian cancer in the 12 years of the study: 11 stage I, three stage II, and three stage III. Van Nagell et al reported that the overall survival of ovarian cancer patients who were screened annually (excluding borderline tumours) at five years was 83.6% (95% CI, 72.8% to 94.4%). They did not report survival according to the stage of disease; however, at the time of publication (2000), all the women with stage I and II disease were alive and well.

The prospective study by Campbell et al (29) aimed to screen 5,000 women at three annual ultrasounds; 4,061 women underwent all three screenings. Three hundred and twenty six women had abnormal ultrasound results and underwent surgery. Nine cases of ovarian cancer were detected in those 326 women. Millo et al (30) also investigated ultrasound as a screening tool but only included 500 women in the study. Twelve women had abnormal ultrasound results, and six women underwent surgery; no cases of ovarian cancer were detected. Millo et al (30) and Campbell et al (29) concluded that ultrasonography seemed to be an effective screening tool for detecting ovarian cancer; however, more high-quality trials were needed to provide evidence for the use of ultrasound. In 2000, Crayford et al (32) published a report of a follow-up study to the Campbell et al study. After 15 years of follow-up, no difference in ovarian cancer mortality between the population of women who had been screened and the general population was detected. Crayford et al (32) also investigated another possible benefit of screening, the ability to monitor benign cysts to see if they became malignant. They did not identify an association between women with benign ovarian cysts and the development of malignant ovarian cancer over the 15-year study period.

Table 5. Studies of ultrasonography alone.

Study	van Nagell, 2000 (35)	Hayashi, 1999 (12)	Tabor, 1994 (19)	Campbell, 1989 (29)	Millo, 1989 (30)
Population	age ≥ 50, post or age ≥ 25, with family history	age ≥ 50	age 46-65	age ≥ 45, (55% post) (4% family history)	age ≥ 45, or post
Type of U/S	transvaginal	transvaginal	transvaginal	transabdominal	transvaginal
# screenings	annually 1987-1999	1 screening	1 screening	3 annual screenings	1 screening
# participants	14,469	23,451	435[a]	5,479	500
# of abnormal U/S tests	180 persisting abnormality	258	54	326	12
# undergoing surgery (%)	180 (1.2%)	95 (0.04%)	9 (2.1%)	326 (5.9%)	6 (1.2%)
# ovarian cancers detected	17 (11 stage I, 3 stage II, 3 stage III)	7 (malignant ovarian cancers)	0	9 (5 stage I, 4 metastatic) (5 at first screen, 4 at second)	0
# false positives	163	88	9	317	6
Positive predictive value	9.4%	7.4%	0	1.5%	0
# cancers developing among women with negative screening tests	4 ovarian cancers detected within 12 months: 2 stage II, 2 stage III	NR	NR	NR	NR

Note: NR, not reported; post, post-menopausal; U/S, ultrasound

[a] There were 950 women included in the study in total; 435 women were randomized to the screening group. Tabor et al (19) did not provide information about the women in the control group.

Colour Doppler imaging (Table 6)

One pilot RCT (20) and two prospective cohort studies (33,34) investigated the effectiveness of colour Doppler imaging (CDI) as a screening test for ovarian cancer in women without a hereditary risk for ovarian cancer. Parkes et al (20) conducted a feasibility study of a randomized trial. Women were either screened with ultrasound, then CDI if the ultrasound was abnormal, or they received no screening at all. Like Tabor et al (19), Parkes et al did not present any detailed information about the control group (20). Initially in the Parkes et al study, women received a second ultrasound instead of CDI. When CDI replaced the second ultrasound, Parkes et al reported that the false positive rate dropped from 2.9% to 0.3%. Admittedly, Parkes et al reported that their study was not powered to assess the effectiveness of CDI on the detection of ovarian cancer; however, they did suggest that their results warranted further investigation of CDI.

Both Vuento et al (33) and Kurjak et al (34) screened women with concurrent ultrasound and CDI. Vuento et al's study only included 1,364 women, 160 of whom had abnormal results. Three women ultimately underwent surgery after persistently abnormal results, and one case of borderline ovarian cancer was detected. The study by Kurjak et al was slightly larger, including over 5,000 women, and reported that 404 women had abnormal test results. Thirty-eight women underwent surgery, and four cases of stage I ovarian cancer were detected. Both studies concluded that ultrasound and CDI were effective screening methods for detecting ovarian cancer; however, Vuento et al suggested that ultrasound alone might be sufficient to detect ovarian cancer.

Table 6. Studies of ultrasonography plus colour Doppler imaging.

Study	Vuento, 1995 (27)	Kurjak,1994 (34)	Parkes,1994 (20)
Population	age 56-61	age 40-71 (56% post)	age 50-64
Screening program	concurrent U/S and CDI	concurrent U/S and CDI	sequential U/S and CDI
# screenings	1 screening	1 screening	1 screening
# participants	1,364	5,013	2,953
# positive screening U/S	160	404	86
# undergoing surgery (%)	3 (0.2%)	38 (0.8%)	9 (0.3%)
# ovarian cancers detected	1 (borderline)	4 (stage I)	1 (stage I)
# false-positives	2	34	8
Positive predictive value	33.3%	10.5%	12.5%
# cancers developing among women with negative screening tests	2 cases within 2 years of screening: 1 stage I ovarian cancer, 1 abdominal carcinomatosis	NR	1 stage I ovarian cancer detected 19 months after screening
Cancers arising during 1 year of follow-up	0	NR	1

Note: CDI, colour Doppler imaging; NR, not reported; post, post-menopausal; U/S, ultrasound

Follow-up studies (Table 7)

Five studies reported follow-up results (21,25,26,32,36), following their trial patients beyond the initial screening period. The pilot RCT by Jacobs et al (21) compared ultrasound screening to no screening and found that, after seven years of follow-up, there were 16 ovarian cancers detected in the screening group compared to 20 cancers in the control group. In the screening group, there were four cases of stage I, one case of stage II, nine cases of stage III, and two cases of stage IV ovarian cancer. In the control group, there were more women diagnosed with advanced stage ovarian cancer: one case each of stage I and stage II disease,

15 cases of stage III ovarian cancer, and three cases of stage IV. Median survival in the screened group was significantly longer than median survival in the control group (72.9 months versus 41.8 months, p=0.0112, respectively). However, this was a pilot study, and a larger trial would have to address whether screening impacts mortality.

Crayford et al (32) reported follow-up results for Campbell et al's (29) cohort study investigating ultrasound alone as an effective screening tool. Campbell et al's study supported the further investigation of ultrasound for ovarian cancer screening. However, Crayford et al reported that after 15 years of follow-up there was no difference in ovarian cancer mortality between the population of women who had been screened and the general population.

Two separate publications (25,36) have reported follow-up results for Jacobs et al's large cohort study of 22,000 women (23). It is important to recall that these patients were also the patients in the Jacobs et al (21) RCT. In Jacobs et al's 1996 follow-up report (36), 49 index cancers (primary epithelial carcinomas of the ovary or fallopian tube) had been identified after follow-up periods ranging from 4.7 to 9.1 years (median 6.7 years). The relative risk of developing an index cancer during the year after screening was 35.9 (95% CI, 18.3 to 70.4) among women with a CA125 level greater than 30U/ml, compared with the entire study population. Women who had CA125 levels less than 30U/ml had a reduced relative risk of 0.13 (95%CI, 0.03 to 0.58) one year after screening. The other follow-up study (25) included only the 741 women with elevated CA125 levels in the original study. In that group of women, 20 cases of ovarian cancer were identified during the follow-up period (6 to 8 years), in addition to the 11 cases of ovarian cancer detected at the initial screening (23). Patients included in this study were followed up annually through a questionnaire asking about hospital visits. If the responses on the questionnaire suggested that the patient was being treated for a gynecologic malignancy, the patient was contacted to gain more information.

Einhorn et al (26) reported follow-up results for their original study (11) of 5,550 women. In addition to the six cases of ovarian cancer identified during screening, 20 cases of ovarian cancer have been detected in the 10 years since the original study was published. Einhorn et al followed patients through a cancer registry in Stockholm searching the registry in 1991, 1993, and 1999 to identify new cases of ovarian cancer among their screened population. Einhorn et al concluded that a trial with a larger sample size and longer follow-up period was needed to determine the effectiveness of ovarian cancer screening with CA125 followed by ultrasound.

Table 7. Follow-up studies.

Study	Crayford, 2000 (32)	Einhorn, 2000 (26)	Menon, 2000 (25)	Jacobs, 1999 (21)	Jacobs, 1996 (36)
Follow-up data for which study	Campbell, 1989 (29)	Einhorn, 1992 (11)	Jacobs, 1993 (23)	Jacobs, 1999 (21)	Jacobs, 1993 (23)
# patients in original study	5,479	5,550	22,000	21,935	22,000
# patients followed-up	5,135 (94%)	NR	741 (women with elevated CA125)	19,960 (91%)	19,464 (88%)
Duration of follow-up	mean 15.5 years	10 years	median 6-8 years	7 years	mean 6.76 years
# ovarian cancers detected in original study	5	6	11	6 screened group	11
# ovarian cancers detected since the original study	20	20	20	16 screened group 20 non-screened group	49

Frequency of screening

No evidence was identified that investigated the effects of different screening intervals on detection rates for ovarian cancer.

Psychological effects of screening

Andersen et al (9) reported results for 3,257 women who responded to a mailed survey regarding their perceived risk of ovarian cancer. They found that women with one relative with ovarian cancer had a perceived higher 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.

There were no studies that investigated the psychological effects of screening on women in the general population; however, a couple of studies have been published about the psychological effects of screening on high-risk populations. Pernet et al (37) 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. Pernet et al 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.

Cull et al (38) administered a questionnaire in a familial ovarian cancer clinic to 196 women. 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 analysis indicated that well-educated (university graduates), anxiety-prone women were more likely to present with high levels of distress regarding their cancer risk.

VI. ONGOING TRIALS

There are three ongoing randomized trials of screening for ovarian cancer in women from the general population. These trials are important as they will attempt to evaluate the impact of screening on mortality and quality of life.

National Institutes of Health Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Trial (http://www.cancer.gov/search/clinical_trials/): This is a randomized study to determine whether screening with CA125 plus transvaginal ultrasound can reduce mortality from ovarian cancer in women aged 55-74. Women in the control group receive standard medical care. A Periodic Survey of Health questionnaire is mailed to each participant annually for 13 years to identify all prevalent and incident cancers, as well as all deaths that occur among both screened and control subjects during the trial. A total of 74,000 women will be recruited. A preliminary report from this study is published (39) but addresses the characteristics of ovarian cysts that might predict for early malignancy and does not address the outcome of screening. This trial is closed.

St. Bartholomew's Randomized Trial of Ovarian Screening: This is a randomized controlled trial to determine whether sequential screening with CA125 and transvaginal ultrasound can reduce mortality from ovarian cancer in postmenopausal women over 50 years of age. A total of 120,000 women will be recruited. Outcomes include mortality from ovarian cancer, psychological acceptability of screening, and cost.

European Randomized Trial of Ovarian Cancer Screening: This is a randomized study with three groups [i) control, ii) transvaginal ultrasound scan every three years, or iii) transvaginal

ultrasound scan every 18 months] designed to determine whether screening can reduce mortality from ovarian cancer in postmenopausal women. A total of 120,000 women will be recruited.

VII. FUTURE RESEARCH

Some researchers are combining several tumour markers to attempt to increase the accuracy of screening tests (5,40,41). Crump et al (5) characterized the behaviour of five tumour markers and determined that the markers behaved independently of each other, which suggests the combined false positive rate from screening with multiple markers may be estimated by the use of individual false positive rates (5). Woolas et al (40) screened 429 women with pelvic masses and concluded that combining multiple tumour markers (CA125, macrophage colony-stimulating factor, OVX1, lipid-associated sialic acid, CA15-3, CA72-4, CA19-9, and CA54/61) increased both specificity and sensitivity. However, when Cane et al (41) specifically studied women at risk for ovarian cancer, they detected that combining tumour markers increases specificity but jeopardizes sensitivity. More high-quality studies are needed to examine the interaction between tumour markers.

Longitudinal screening algorithms using novel tumour markers also need to be developed. Petricoin et al (42) 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. INTERPRETIVE SUMMARY

The evidence available regarding screening postmenopausal women for ovarian cancer is limited. Cohort studies provide data on the positive predictive value of screening but little on the sensitivity of CA125 and ultrasound as screening tests. None of these strategies has demonstrated sufficiently acceptable performance characteristics (sensitivity, specificity, or predictive values) to justify their use as screening tests for the general population at standard risk.

From cohort studies, the sensitivity of CA125 and ultrasonography appears to be in the range of 80 to 100%, but these screening tests have low positive predictive values resulting in healthy women being recalled for further testing and assessment. Between 0.01% and 2.0% of women participating in CA125-based screening programs will undergo surgery but will not have any cancer detected. The proportion of women without evident cancer who have investigational surgery following screening with ultrasound alone appears to be higher (0.04% to 5.8%).

Since the five-year overall survival of women with advanced ovarian cancer is only 30% (3), but 80% to 90% for women with stage I disease (4) the hope is that screening will increase survival through the earlier detection and treatment of disease. In the follow-up component to Jacobs et al's (23) cohort study of 22,000 women, 49 cases of ovarian cancer were detected over a mean of 6.76 years. There were 29 cases (59%) of advanced ovarian cancer (stage III-IV), four of stage II ovarian cancer, and 16 of stage I ovarian cancer. Jacobs et al did not report survival data for the women diagnosed with ovarian cancer.

The subsequent RCT by Jacobs et al (21) did report survival. They suggested that screening with ultrasound and CA125 can detect early ovarian cancer, which might translate into longer survival for women whose cancers are detected by screening. However, they do admit that while "survival differed significantly between women with index cancers in the screened and control groups,…this finding is not definitive evidence for a benefit from screening for ovarian cancer….".

In summary, the data available from the RCT by Jacobs et al (21) suggest that of every 10,000 women participating in an annual screening program with CA125 for three years:

- 800 will have an ultrasound scan because of an elevated CA125,
- 30 will undergo a surgical investigation because of an abnormal ultrasound result,

- Of that 30, six will have ovarian cancer detected (approximately half of these will be early-stage disease), and 24 will be determined not to have ovarian cancer,
- 10 will have ovarian cancer detected over the next eight years.

Put in terms of benefits and harms, for every 10,000 women screened, six will have their cancer detected and treated (only half of these stand a chance of cure), and 24 will undergo unnecessary surgery. There may also be harm associated with receiving abnormal test results and having to return for confirmatory tests. Survival benefits are unknown but might be expected for the three of 10,000 asymptomatic women found with early-stage cancers.

No single ovarian cancer-screening test achieves a high level of specificity, and therefore, many women will undergo laparoscopy or laparotomy for each case of ovarian cancer diagnosed. In addition, not all ovarian cancer diagnosed in a screened asymptomatic population is early and possibly curable stage disease, thus further undermining the effectiveness of the screening tests.

Epithelial ovarian cancer is a lethal, infrequent cancer with a presumably short natural history, no detectable pre-malignant phase, a lack of early stage symptoms, perceptions of high risk, and screening tests with low positive predictive values. Because of these facts, screening for ovarian cancer remains a frustrating challenge to clinicians wanting to detect the disease early enough in the asymptomatic population to improve overall survival without increasing morbidity.

In summary, there is insufficient evidence currently to support the introduction of screening for ovarian cancer in the asymptomatic general-risk postmenopausal population. Screening is associated with increased rates of surgery and patient anxiety. Currently, screening asymptomatic postmenopausal women for ovarian cancer does not meet the WHO's effective screening criteria: the benefits of screening in terms of lives saved, pain, and suffering with the current screening tests available do not appear to be outweighed by the social costs of unnecessary investigations and treatments. That the detection of early-stage cancers leads to increased survival rates remains to be proved.

IX. OPINIONS OF THE GYNECOLOGY DISEASE SITE GROUP

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:

- There is insufficient evidence currently to support the introduction of screening in the asymptomatic, general-risk, postmenopausal population.
- Screening is associated with increased rates of surgery and patient anxiety.
- The benefits of screening in terms of lives saved, pain, and suffering do not appear to be outweighed by the social costs of unnecessary investigations and treatments.
- Detection of early-stage cancers may not lead to increased survival rates.
- No optimal interval for screening can be defined.
- The positive predictive value of the screening tests needs to be improved.
- Any further recommendations regarding screening for ovarian cancer in this group of women must await the conclusions of the three major ongoing trials.
- Efforts to impact ovarian cancer-related mortality rates should in the meantime focus on prevention, including:
    a) Identifying women at high risk followed by genetic counselling and BRCA1 and BRCA2 identification (Appendix 2). The use of prophylactic oophorectomy in identified BRCA1 or 2 carriers needs to be further explored.
    b) Making available to both patients and health care providers information about the benefits of oral contraceptive use and tubal ligation in prevention.

X. RELATED EVIDENCE SUMMARIES

Practice Guidelines Initiative's Evidence Summary Reports:

- #4-4 *Management Options for Women with a Hereditary Predisposition to Ovarian Cancer*
- #4-6b *Screening High-Risk Women for Ovarian Cancer (in progress)*

XI. EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT

Practitioner Feedback

A 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 eighty practitioners in Ontario (41 medical oncologists, 2 surgeons, 16 gynecologists and 21 family physicians). The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. The practitioner feedback survey was mailed out on November 21, 2002. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The Gynecology DSG reviewed the results of the survey.

Results

Thirty-four responses were received out of the 79 surveys sent (43% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 23 indicated that the report was relevant to their clinical practice and they completed the survey. Results of the practitioner feedback survey are summarized in Table 8.

Table 8. 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.	20 (93%)	3 (7%)	0
There is a need for an evidence summary on this topic.	20 (87%)	1 (4%)	2 (9%)
The literature search is relevant and complete in this evidence summary.	19 (83%)	4 (17%)	0
I agree with the methodology used to summarize the evidence.	22 (96%)	1 (4%)	0
I agree with the overall interpretation of the evidence in the evidence summary.	23 (100%)	0	0
The *Opinions of the Disease Site Group* section of this evidence summary is useful.	21 (91%)	2 (9%)	0
An evidence summary of this type will be useful for clinical decision making.	20 (87%)	2 (9%)	1 (4%)
At present, there is insufficient evidence to develop a practice guideline on this topic.	10 (43%)	4 (17%)	9 (40%)
There is a need to develop an evidence-based practice guideline on this topic when sufficient evidence becomes available.	20 (95%)	1 (5%)	0

Summary of Written Comments

Four respondents (17%) provided written comments. The respondents provided positive feedback regarding the evidence summary: "excellent review", "very thorough" and "extremely well-argued" were some of the comments. There were no suggestions provided to modify the evidence summary.

Practice Guidelines Coordinating Committee Approval Process

The evidence summary report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. Twelve of fifteen members of the PGCC returned ballots. All twelve PGCC members approved the evidence summary report as written. Overall, the PGCC was pleased with the evidence summary, however they did suggest a few editorial changes that would clarify the evidence summary. The Gynecology DSG members reviewed the suggestions and modified the text of the evidence summary.

XII. PEER REVIEW PROCESS

In May 2003, the Gynecology Cancer DSG submitted a manuscript of this evidence summary (formatted as a systematic review) to the *Canadian Medical Association Journal (CMAJ)*. The *CMAJ* decided not the accept the manuscript for publication; however, they did provide very thorough feedback for the manuscript. The manuscript was revised and then submitted to the *Journal of Obstetrics and Gynaecology Canada* in October 2003.

Peer review comments

1. In large screening studies, several articles are published—it is important that they are not interpreted as separate studies.
2. There is insufficient evidence describing how the women were followed after screening.
3. It is important to indicate the number of women who developed cancer who had negative screening tests.

Modifications to the evidence summary based on peer review comments

1. Table 2 was modified to indicate which studies investigated the same patient population. The results section was rewritten to indicate which studies were using the same patient data. Menon et al (25) and Jacobs et al (1988) (43) were removed from Table 3 because the study by Jacobs et al (1993) (23) included the same patient population. DePriest et al (44), van Nagell et al (1990) (45), and van Nagell et al (1995) (46) were removed from Table 5 because van Nagell et al (2000) (35) included all the same patients in that trial. Goswamy et al (47) was also removed from Table 5 because that study included the same patients as Campbell et al (29). Hayashi et al (12) and Einhorn et al (11) were added as new evidence.
2. A section was added to the evidence summary specifically addressing the follow-up of women after screening tests.
3. Subheadings were added to Tables 3 through 6 indicating the number of cancers identified among women who had negative screening tests, the number of screenings each woman underwent, and the number of abnormal CA125 and/or ultrasound tests reported.

XIII. JOURNAL REFERENCE

In August 2004 a systematic review of the evidence presented in this evidence summary was published in the *Journal of Obstetrics and Gynaecology Canada*:

Fung Kee Fung M, Bryson P, Johnston M, Chambers A. Screening postmenopausal women for ovarian cancer: A systematic review. J Obstet Gynaecol Can. 2004;26:717-28.

XIV. ACKNOWLEDGMENTS

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For a full list of members of the Practice Guidelines Coordinating Committee and the Gynecology Disease Site Group, please visit the CCO Web site at http://www.cancercare.on.ca/access_PEBC.htm.

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Appendix 1. 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 tumour on the external surface; capsule intact
- 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 equals 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.