Supplementary Online Content

Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. doi:10.1001/jama.2017.21421

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Literature Search Strategies for Primary Literature

Key:
/ = MeSH subject heading
$ = truncation
* = truncation
? = wildcard
ab = word in abstract
adj# = adjacent within x number of words
ae = adverse effects
hw = subject heading word
id = identifier
kw = keyword
md = methodology
near/# = adjacent within x number of words
ti = word in title

Cochrane Central Register of Controlled Trials (CENTRAL)

#1   (ovar or (fallopian next tub*) or adenx*):ti,ab,kw near/4 (cancer* or neoplas* or tumo* or malignan* or carcinoma* or adenocarcinoma* or mass*):ti,ab,kw*

#2   screen:ti,ab,kw*

#3   detect:ti*

#4   (sonog or ultraso*):ti,ab,kw*

#5   (tumo next marker*):ti,ab,kw*

#6   (serum next cancer next antigen):ti,ab,kw*

#7   "CA 125":ti,ab,kw

#8   #1-#7

#9   #1 and #8 Publication Year from 2003 to 2016, in Trials

MEDLINE

1   Ovarian Neoplasms/

2   Fallopian Tube Neoplasms/

3   ((ovar$ or fallopian tub$ or adenx$) adj4 (cancer$ or neoplas$ or tumo$ or malignan$ or carcinoma$ or adenocarcinoma$ or mass$)).ti,ab.

4   or/1-3

5   Mass screening/

6   "Early detection of cancer"/

7   (screen$ adj5 (ovar$ or fallopian tub$ or adnex$)).ti,ab.

8   detect$.ti.

9   Ultrasonography/

10   (sonog$ or ultraso$).ti,ab.

11   Tumor Markers, Biological/

12   tumo?r marker$.ti,ab.

13   serum cancer antigen$.ti,ab.

14   CA 125.ti,ab.

15   algorithm$.ti,ab.

16   ROCA.ti,ab.

17   or/5-16

18   4 and 17

19   Ovarian Neoplasms/us [Ultrasonography]

20   Fallopian Tube Neoplasms/us [Ultrasonography]

21   18 or 19 or 20

22   clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled

trials as topic/ or meta-analysis as topic/
23 *(clinical trial or controlled clinical trial or meta analysis or randomized controlled trial).pt.*
24 *Random$.ti,ab.*
25 *control groups/ or double-blind method/ or single-blind method/*
26 *clinical trial$.ti,ab.*
27 *controlled trial$.ti,ab.*
28 *meta analy$.ti,ab.*
29 *or/22-28*
30 *21 and 29*
31 *Animals/ not (Humans/ and Animals/)*
32 *30 not 31*
33 *limit 32 to (english language and yr="2003 -Current")*
34 *remove duplicates from 33*

PUBMED, *publisher-supplied records*
#14 Search (((#13) AND publisher[sb]) AND ("2003/01/01"[Date - Publication] : "3000"[Date - Publication])) AND English[Language]
#13 Search #8 AND #12
#12 Search #9 OR #10 OR #11
#11 Search (control[tiab] OR controls[tiab] OR controlled[tiab] OR controled[tiab]) AND (trial[tiab] OR trials[tiab])
#10 Search "clinical trial"[tiab] OR "clinical trials"[tiab] OR random[tiab]*
#9   Search systematic review[sb] OR metaanaly[tiab] OR meta analysis[tiab]*
#8   Search #1 AND #7
#7   Search #2 OR #3 OR #4 OR #5 OR #6
#6   Search CA 125[tiab]
#5   Search serum cancer antigen[tiab]*
#4   Search tumo marker*[tiab]*
#3   Search sonog[tiab] or ultraso*[tiab]*
#2   Search screen[tiab] OR detect*[tiab]*
#1   Search (ovar[tiab] or fallopian tub*[tiab] or adenx*[tiab]) AND (cancer*[tiab] or neoplas*[tiab] or tumor*[tiab] OR tumour*[tiab] or malignan*[tiab] or carcinoma*[tiab] or adenocarcinoma*[tiab] or mass*[tiab])*

eTable 1. Inclusion and Exclusion Criteria

Category	Included	Excluded
Aim	Screening for ovarian cancer in a primary care setting (alone or as part of a clinical examination)	Screening for ovarian cancer in selected high-risk populations, such as women who are BRCA mutation carriers or patients of a specialty practice, such as oncology
Populations	Asymptomatic, average risk women, ages 45 years and older	Trials enrolling only women who are selected based on an increased risk for ovarian cancer (e.g. known predisposing genetic syndromes, strong family history)
Screening tests	Screening tests and approaches evaluated in clinical trials such as, but not limited to: testing for serum cancer antigen (CA–125), transvaginal ultrasonography, and combined screening approaches or algorithms	Screening tests not evaluated in clinical trials
Comparisons	Comparison of screening with usual care or no screening; comparison of different included screening methods or programs	
Outcomes	**KQ 1:** Ovarian cancer–specific mortality (including primary peritoneal and fallopian tube cancer), all-cause mortality, cancer-related morbidity, and quality of life. **KQ 2:** Surgery rate, rates of false-positive screening results, complications of diagnostic surgical procedures, and health and psychological effects of screening tests	
Settings	Primary care settings, including obstetrics/gynecology practices	Specialty practice settings, such as oncology
Study designs	Randomized, controlled trials	Cohort studies, case-controls, case reports, case series, and decision analyses
Study quality	Good and fair quality according to USPSTF criteria and supplemented quality measures	Poor quality according to USPSTF criteria and supplemental quality measures
Language	English	Non–English language studies

Abbreviations: USPSTF, United States Preventive Services Task Force

eTable 2. Quality Assessment Criteria of Randomized Controlled Trials[a]

USPSTF quality rating criteria[1]
• Initial assembly of comparable groups employs adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
• Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
• Important differential loss to followup or overall high loss to followup
• Measurements: equal, reliable, and valid (includes masking of outcome assessment)
• Clear definition of the interventions
• All important outcomes considered
• Intention-to-treat analysis

[a] Good quality studies generally meet all quality criteria. Fair quality studies do not meet all the criteria but not have critical limitations that could invalidate study findings. Poor quality studies have a single fatal flaw or multiple important limitations that could invalidate study findings. Critical appraisal of studies using a priori quality criteria are conducted independently by at least two reviewers. Disagreements in final quality assessment are resolved by consensus, and, if needed, consultation with a third independent reviewer

Abbreviations: USPSTF, U.S. Preventive Services Task Force

eTable 3. Harms Reported in Ovarian Cancer Screening Trials: Psychological Effects of Screening

Trial, Author, Year of publication	UKCTOCS (Barrett, 2014)[2]		QUEST, 2007[3]
Quality	Good		Fair
Measures	Spielberger State/Trait Anxiety Inventory General Health Questionnaire 12		SF-36 Mental and Physical Health scores (quality of life) Impact of Events Scale (distress) Modified Lerman cancer worry scale (cancer worry)
Population	Random sample from UKCTOCS	Event sample: All women in the screening arms recalled for repeat screening[a]	All participants
N analyzed	CA-125 ROCA: 301 TVU: 283 Control: 755	CA-125 ROCA: 12,357 TVU: 9,678	Screening group: 292 Control: 150
Psychological effect of screening	Random sample: no evidence of difference in state anxiety between screening and control groups (P= 0.2)	NA	No statistically significant differences between study arms in measures of quality of life, distress, or cancer worry (P = NR)
Psychological effects of positive test results or repeat screening tests	No evidence of change in anxiety (P= 0.36) or psychological morbidity (P= 0.96) due to repeat screenings compared with annual screen	Evidence of higher anxiety for multiple repeat scans (p<0.010) (small absolute effect)[b] compared with a single repeat screen Greater odds of psychological morbidity (GHQ-12: score $\geq$ 4) with higher level referral screening: OR 1.28 (95% CI, 1.18 to 1.39)[c]	Women with abnormal test results (N= 32) compared with women with no abnormal results more likely to report increased levels of cancer worry at 2-year followup: OR 2.8 (95% CI, 1.1 to 7.2)

[a] Excluding those in the random sample analysis

[b] Difference in Spielberger State/Trait Anxiety Inventory score (range 20-80 points): 0.37 (95% CI 0.23 0.51; P < 0.01)

[c] Higher level referral- CA-125 ROCA: repeat blood test and a transvaginal scan, TVU: repeat scan or biopsy

Abbreviations: CG = control group; CI = confidence interval; GHQ-12 = General Health Questionnaire 12; NR= not reported; OR = odds ratio; QoL = quality of life; QUEST = Quality of life, Education, and Screening Trial; ROCA = Risk of Ovarian Cancer Algorithm TVU = transvaginal ultrasound; SF-36 = 36-Item Short Form Survey; UKCTOCS = U.K. Collaborative Trial of Ovarian Cancer Screening

eReferences

1. U.S. Preventive Services Task Force. *U.S. Preventive Services Task Force Procedure Manual.* Rockville, MD: U.S. Preventive Services Task Force; 2015.

2. Barrett J, Jenkins V, Farewell V, et al. Psychological morbidity associated with ovarian cancer screening: results from more than 23,000 women in the randomised trial of ovarian cancer screening (UKCTOCS). *BJOG.* 2014;121(9):1071-1079.

3. Andersen MR, Drescher CW, Zheng Y, et al. Changes in cancer worry associated with participation in ovarian cancer screening. *Psychooncology.* 2007;16(9):814-820.