Ovarian Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Lutz AM, Willmann JK, Drescher CW, et al. Early diagnosis of ovarian carcinoma: is a solution in sight? Radiology. 2011; 259(2):329-345.	Review/Other-Dx	N/A	To review serum biomarkers and imaging tests for the early detection of ovarian cancer and provide an outlook on the potential improvements in these noninvasive diagnostic tools that may lead to successful implementation in a screening program.	TVUS is an already established first-line imaging modality in the diagnostic work-up of ovarian lesions and is therefore widely available. TVUS costs less than other imaging modalities, has reasonable diagnostic performance, and has the potential for improving sensitivity and specificity with the application of molecularly targeted microbubbles. These facts render US the most likely imaging tool to be successful for screening purposes.	4

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2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.	Review/Other-Dx	N/A	To estimate the numbers of new cancer cases and deaths that will occur in the United States in the current year and compile the most recent data on cancer incidence, mortality, and survival.	Mortality data were collected by the National Center for Health Statistics. In 2017, 1,688,780 new cancer cases and 600,920 cancer deaths are projected to occur in the United States. For all sites combined, the cancer incidence rate is 20% higher in men than in women, while the cancer death rate is 40% higher. However, sex disparities vary by cancer type. For example, thyroid cancer incidence rates are 3-fold higher in women than in men (21 vs 7 per 100,000 population), despite equivalent death rates (0.5 per 100,000 population), largely reflecting sex differences in the "epidemic of diagnosis." Over the past decade of available data, the overall cancer incidence rate (2004-2013) was stable in women and declined by approximately 2% annually in men, while the cancer death rate (2005-2014) declined by about 1.5% annually in both men and women. From 1991 to 2014, the overall cancer death rate dropped 25%, translating to approximately 2,143,200 fewer cancer deaths than would have been expected if death rates had remained at their peak. Although the cancer death rate was 15% higher in blacks than in whites in 2014, increasing access to care as a result of the Patient Protection and Affordable Care Act may expedite the narrowing racial gap; from 2010 to 2015, the proportion of blacks who were uninsured halved, from 21% to 11%, as it did for Hispanics (31% to 16%). Gains in coverage for traditionally underserved Americans will facilitate the broader application of existing cancer control knowledge across every segment of the population.	4

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3. Brown PO, Palmer C. The preclinical natural history of serous ovarian cancer: defining the target for early detection. PLoS Med. 2009; 6(7):e1000114.	Review/Other-Dx	N/A	To examine available reports on occult serous ovarian cancer and develop mathematical models describing the early natural history of ovarian cancer.	The analysis yielded several critical insights into the early natural history of serous ovarian cancer. First, these cancers spend on average more than 4 years as in situ, stage I, or stage II cancers and approximately 1 year as stage III or IV cancers before they become clinically apparent. Second, for most of the occult period, serous cancers are <1 cm in diameter, and not visible on gross examination of the ovaries and Fallopian tubes. Third, the median diameter of a serous ovarian cancer when it progresses to an advanced stage (stage III or IV) is about 3 cm. Fourth, to achieve 50% sensitivity in detecting tumors before they advance to stage III, an annual screen would need to detect tumors of 1.3 cm in diameter; 80% detection sensitivity would require detecting tumors <0.4 cm in diameter. Fifth, to achieve a 50% reduction in serous ovarian cancer mortality with an annual screen, a test would need to detect tumors of 0.5 cm in diameter. The analysis has formalized essential conditions for successful early detection of serous ovarian cancer.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
4. Havrilesky LJ, Sanders GD, Kulasingam S, et al. Development of an ovarian cancer screening decision model that incorporates disease heterogeneity: implications for potential mortality reduction. Cancer. 2011; 117(3):545-553.	Review/Other-Dx	N/A	To estimate the impact of a 2-phenotype paradigm of epithelial ovarian cancer on the mortality reduction achievable using available screening technologies.	In validation against United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) data, the model-predicted percentage of screen-detected cancers diagnosed at stage I and II was 41% compared with 47% (UKCTOCS data), and the model-predicted PPV of screening was 27% compared with 35% (UKCTOCS data). The model-estimated PPV of a strategy of annual population-based screening in the United States at ages 50 to 85 years was 14%. The mortality reduction using annual postmenopausal screening was 14.7% (1-phenotype model) and 10.9% (2-phenotype model). Mortality reduction was lower with the 2-phenotype model than with the 1-phenotype model regardless of screening frequency or test sensitivity; 68% of cancer deaths are accounted for by the aggressive phenotype. The current analysis suggested that reductions in ovarian cancer mortality using available screening technologies on an annual basis are likely to be modest. A model that incorporated 2 clinical phenotypes of ovarian carcinoma into its natural history predicted an even smaller potential reduction in mortality because of the more frequent diagnosis of indolent cancers at early stages.	4
5. Kurman RJ, Visvanathan K, Roden R, Wu TC, Shih Ie M. Early detection and treatment of ovarian cancer: shifting from early stage to minimal volume of disease based on a new model of carcinogenesis. Am J Obstet Gynecol. 2008; 198(4):351-356.	Review/Other-Dx	N/A	Propose a new model of ovarian carcinogenesis based on clinical, pathological, and molecular genetic studies that may enable more targeted screening and therapeutic intervention to be developed. The model divides ovarian cancer into 2 groups designated type I and type II.	Screening tests that focus on stage I disease may detect low-grade type I neoplasm but miss the more aggressive type II tumors, which account for most ovarian cancers.	4
6. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011; 43(5):420-432.	Review/Other-Dx	N/A	To review the major subtypes of ovarian carcinoma.	No results stated.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Soslow RA. Histologic subtypes of ovarian carcinoma: an overview. Int J Gynecol Pathol. 2008; 27(2):161-174.	Review/Other-Dx	N/A	Review the prevalence, morphology, immunophenotype and, in some cases, genotype of each major ovarian cancer subtype.	No results stated.	4
8. Crum CP, Drapkin R, Kindelberger D, Medeiros F, Miron A, Lee Y. Lessons from BRCA: the tubal fimbria emerges as an origin for pelvic serous cancer. Clin Med Res. 2007; 5(1):35-44.	Review/Other-Dx	N/A	Emerging studies that carefully examine the fallopian tubes suggest a high frequency of early cancer in the fimbria in unselected women with ovarian and peritoneal serous carcinoma, raising the distinct possibility that a significant proportion of these tumors have a fimbrial origin. The evidence for these discoveries and their relevance to serous cancer classification, early detection and prevention are addressed in this review.	A model for pelvic serous cancer is proposed that takes into account five distinct variables which ultimately impact on origin and tumor distribution: 1) location of target epithelium, 2) genotoxic stress, 3) type of epithelium, 4) mitigating genetic factors, and 5) tumor spread pattern.	4
9. Clarke-Pearson DL. Clinical practice. Screening for ovarian cancer. N Engl J Med. 2009; 361(2):170-177.	Review/Other-Dx	N/A	Review the usefulness of screening for ovarian cancer.	Routine screening of the general population for ovarian cancer is not recommended. Studies show that screening with serum tumor markers (especially CA-125), ovarian imaging with TVUS or a multimodal strategy can detect ovarian cancer at an earlier stage, but trials that have been completed to date have not included a control group for direct comparison. There is no trial that has yet shown improved overall survival for women undergoing screening.	4
10. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol. 2007; 25(11):1329-1333.	Meta-analysis	10 studies	Meta-analysis was performed to facilitate clinical management and counseling of individuals at high risk of carrying a BRCA1 or BRCA2 mutation.	Meta-analytic mean cumulative cancer risks for mutation carriers at age 70 years were as follows: breast cancer risk of 57% (95% CI, 47% to 66%) for BRCA1 and 49% (95% CI, 40% to 57%) for BRCA2 mutation carriers; and ovarian cancer risk of 40% (95% CI, 35% to 46%) for BRCA1 and 18% (95% CI, 13% to 23%) for BRCA2 mutation carriers.	M
11. ACOG Practice Bulletin No. 103: Hereditary breast and ovarian cancer syndrome. Obstet Gynecol. 2009;113(4):957-966.	Review/Other-Dx	N/A	To provide guidelines for hereditary breast and ovarian cancer syndrome.	No results listed in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Jacobs I, Bast RC, Jr. The CA 125 tumour-associated antigen: a review of the literature. Hum Reprod. 1989; 4(1):1-12.	Review/Other-Dx	N/A	Review literature on the nature, distribution and clinical significance of CA 125.	Despite limitations of sensitivity and specificity serum CA 125 estimation is of clinical value in the pre-operative diagnosis and monitoring of ovarian malignancy and may be a prognostic indicator for this disease. The role of CA 125 in screening for early-stage ovarian cancer is currently under investigation. Recent reports suggest that serum CA 125 measurement may also be of value as a prognostic indicator in endometrial cancer and as a reflection of disease status in advanced endometriosis.	4
13. Committee Opinion No. 477: the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer. Obstet Gynecol. 2011; 117(3):742-746.	Review/Other-Dx	N/A	Guideline on the role of the obstetrician-gynecologist in the early detection of epithelial ovarian cancer.	Evaluation of the symptomatic patient includes physical examination and may include TVUS and measurement of levels of the serum tumor marker CA 125. Patients suspected of having ovarian cancer should be managed by a gynecologic surgeon, such as a gynecologic oncologist, who is trained to perform comprehensive surgical staging and cytoreductive (debulking) surgery.	4
14. Daniilidis A, Karagiannis V. Epithelial ovarian cancer. Risk factors, screening and the role of prophylactic oophorectomy. Hippokratia. 2007; 11(2):63-66.	Review/Other-Dx	N/A	To review recent studies on risk factors, screening and the value of prophylactic oophorectomy in high risk women for ovarian cancer.	No results stated in abstract.	4

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Reade CJ, Riva JJ, Busse JW, Goldsmith CH, Elit L. Risks and benefits of screening asymptomatic women for ovarian cancer: a systematic review and meta-analysis. Gynecol Oncol. 2013;130(3):674-681.	Meta-analysis	10 trials	To perform a systematic review and meta-analysis to quantify risks and benefits of screening asymptomatic women for ovarian cancer.	Ten randomized trials proved eligible. Screening did not reduce all-cause mortality (relative risk (RR)=1.0, 95% confidence interval (CI) 0.96-1.06), ovarian cancer specific mortality (RR=1.08, 95% CI 0.84-1.38), or risk of diagnosis at an advanced stage (RR of diagnosis at FIGO stages III-IV=0.86, 95% CI 0.68-1.11). Transvaginal ultrasound resulted in a mean of 38 surgeries per ovarian cancer detected (95% CI 15.7-178.1) while screening with CA-125 led to 4 surgeries per ovarian cancer detected (95% CI 2.7-4.5). Surgery was associated with severe complications in 6% of women (95% CI 1%-11%). Quality of life was not affected by screening; however, women with false-positive results had increased cancer-specific distress compared to those with normal results (odds ratio (OR)=2.22, 95% CI 1.23-3.99).	M
16. Jacobs IJ, Skates SJ, MacDonald N, et al. Screening for ovarian cancer: a pilot randomised controlled trial. Lancet. 1999; 353(9160):1207-1210.	Experimental-Dx	Screened group (n=10,958) Control group (n=10,977)	Pilot randomized trial to assess multimodal screening with sequential CA 125 antigen and US.	Of 468 women in the screened group with a raised CA 125, 29 were referred for a gynaecological opinion; screening detected an index cancer in 6 and 23 had false-positive screening results. The PPV was 20.7%. During 7-year follow-up, 10 further women with index cancers were identified in the screened group and 20 in the control group. Median survival of women with index cancers in the screened group was 72.9 months and in the control group was 41.8 months (P=0.0112). The number of deaths from an index cancer did not differ significantly between the control and screened groups (18/10,977 vs 9/10,958, relative risk 2.0 [95% CI, 0.78-5.13]). Results show that a multimodal approach to ovarian cancer screening in a randomized trial is feasible and justify a larger randomized trial to see whether screening affects mortality.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
17. Kobayashi H, Yamada Y, Sado T, et al. A randomized study of screening for ovarian cancer: a multicenter study in Japan. Int J Gynecol Cancer. 2008; 18(3):414-420.	Experimental-Dx	Intervention group (n=41,688) Control group (n=40,799)	Prospective randomized controlled trial of ovarian cancer screening to establish an improved strategy for the early detection of cancers.	27 cancers were detected in the 41,688-screened women. 8 more cancers were diagnosed outside the screening program. Detection rates of ovarian cancer were 0.31 per 1,000 at the prevalent screen and 0.38-0.74 per 1,000 at subsequent screens; they increased with successive screening rounds. Among the 40,779 control women, 32 women developed ovarian cancer. The proportion of stage I ovarian cancer was higher in the screened group (63%) than in the control group (38%), which did not reach statistical significance (P=0.2285). The rise in the detection of early-stage ovarian cancer in asymptomatic postmenopausal women is not significant, but future decisions on screening policy should be informed by further follow-up from this trial.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. Buys SS, Partridge E, Black A, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. JAMA. 2011; 305(22):2295-2303.	Experimental-Dx	78,216 women assigned to either annual screening (n=39,105) or usual care (n=39,111)	To evaluate the effect of screening for ovarian cancer on mortality in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.	Ovarian cancer was diagnosed in 212 women (5.7 per 10,000 person-years) in the intervention group and 176 (4.7 per 10,000 person-years) in the usual care group (rate ratio, 1.21; 95% CI, 0.99-1.48). There were 118 deaths caused by ovarian cancer (3.1 per 10,000 person-years) in the intervention group and 100 deaths (2.6 per 10,000 person-years) in the usual care group (mortality rate ratio, 1.18; 95% CI, 0.82-1.71). Of 3,285 women with false-positive results, 1,080 underwent surgical follow-up; of whom, 163 women experienced at least one serious complication (15%). There were 2,924 deaths due to other causes (excluding ovarian, colorectal, and lung cancer) (76.6 per 10,000 person-years) in the intervention group and 2,914 deaths (76.2 per 10,000 person-years) in the usual care group (rate ratio, 1.01; 95% CI, 0.96-1.06). Among women in the general US population, simultaneous screening with CA-125 and TVUS compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Partridge E, Kreimer AR, Greenlee RT, et al. Results from four rounds of ovarian cancer screening in a randomized trial. Obstet Gynecol. 2009; 113(4):775-782.	Experimental-Dx	34,261 women	Randomized trial to test whether annual screening with TVUS and CA-125 reduces ovarian cancer mortality.	Among 34,261 screening arm women without prior oophorectomy, compliance with screening ranged from 83.1% (T0) to 77.6% (T3). Screen positivity rates declined slightly with TVUS, from 4.6 at T0 to 2.9-3.4 at T1-T3; CA 125 positivity rates (range 1.4%-1.8%) showed no time trend. 89 invasive ovarian or peritoneal cancers were diagnosed; 60 were screen detected. PPV and cancer yield per 10,000 women screened on the combination of tests were similar across screening rounds (range 1.0%-1.3% for PPV and 4.7-6.2 for yield); however, the biopsy (surgery) rate among screen positives decreased from 34% at T0 to 15-20% at T1-T3. The overall ratio of surgeries to screen-detected cancers was 19.5:1. 72% of screen-detected cases were late stage (III/IV). Through 4 screening rounds, the ratio of surgeries to screen-detected cancers was high, and most cases were late stage. However, the effect of screening on mortality is as yet unknown.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
20. van Nagell JR, Jr., Miller RW, DeSimone CP, et al. Long-term survival of women with epithelial ovarian cancer detected by ultrasonographic screening. Obstet Gynecol. 2011;118(6):1212-1221.	Observational-Dx	37,293 women	To estimate the effect of ultrasonographic screening on stage at detection and long-term disease-specific survival of women with epithelial ovarian cancer.	Forty-seven invasive epithelial ovarian cancers and 15 epithelial ovarian tumors of low malignant potential were detected. No women with low malignant potential tumors experienced recurrent disease. Stage distribution for invasive epithelial cancers was: stage I, 22 (47%); stage II, 11 (23%); stage III, 14 (30%), and stage IV, 0 (0%). Follow-up varied from 2 months to 20.1 years (mean, 5.8 years). The 5-year survival rate for invasive epithelial ovarian cancers detected by screening was: stage I, 95%+/-4.8%; stage II, 77.1%+/-14.5%; and stage III, 76.2%+/-12.1%. The 5-year survival rate for all women with invasive epithelial ovarian cancer detected by screening as well as interval cancers was 74.8%+/-6.6% compared with 53.7%+/-2.3% for unscreened women with ovarian cancer from the same institution treated by the same surgical and chemotherapeutic protocols (P<.001).	3
21. van Nagell JR, Jr., DePriest PD, Ueland FR, et al. Ovarian cancer screening with annual transvaginal sonography: findings of 25,000 women screened. Cancer. 2007; 109(9):1887-1896.	Observational-Dx	25,327 women	Analysis of patients in an ovarian cancer screening project to determine the value of annual TVUS as a screening method for ovarian cancer.	TVUS had sensitivity of 85%, specificity of 98.7%, PPV of 14.01%, and NPV of 99.9%. TVUS screening, when performed annually, was associated with a decrease in disease stage at detection and with case-specific ovarian cancer mortality, but it was not effective in detecting ovarian cancers in women who had normal ovarian volume.	3

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22. Lu KH, Skates S, Hernandez MA, et al. A 2-stage ovarian cancer screening strategy using the Risk of Ovarian Cancer Algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. Cancer. 2013;119(19):3454-3461.	Observational-Dx	4051 women	To determine if this 2-step strategy has sufficiently high specificity and PPV for screening postmenopausal women at general population risk in the U.S.	A total of 4051 women participated over 11 years. The average annual rate of referral to a CA125 test in 3 months was 5.8%, and the average annual referral rate to TVS and review by a gynecologic oncologist was 0.9%. Ten women underwent surgery on the basis of TVS, with 4 invasive ovarian cancers (1 with stage IA disease, 2 with stage IC disease, and 1 with stage IIB disease), 2 ovarian tumors of low malignant potential (both stage IA), 1 endometrial cancer (stage I), and 3 benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval = 12.2%, 73.8%) for detecting invasive ovarian cancer. The specificity was 99.9% (95% confidence interval = 99.7%, 100%). All 4 women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA125 test values prior to rising CA125 levels.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
23. Jacobs IJ, Menon U, Ryan A, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. Lancet. 2015:[E-pub ahead of print].	Observational-Dx	202, 638 women	To establish the effect of early detection by screening on ovarian cancer mortality.	Between June 1, 2001, and Oct 21, 2005, we randomly allocated 202 638 women: 50 640 (25.0%) to MMS, 50 639 (25.0%) to USS, and 101 359 (50.0%) to no screening. 202 546 (>99.9%) women were eligible for analysis: 50 624 (>99.9%) women in the MMS group, 50 623 (>99.9%) in the USS group, and 101 299 (>99.9%) in the no screening group. Screening ended on Dec 31, 2011, and included 345 570 MMS and 327 775 USS annual screening episodes. At a median follow-up of 11.1 years (IQR 10.0-12.0), we diagnosed ovarian cancer in 1282 (0.6%) women: 338 (0.7%) in the MMS group, 314 (0.6%) in the USS group, and 630 (0.6%) in the no screening group. Of these women, 148 (0.29%) women in the MMS group, 154 (0.30%) in the USS group, and 347 (0.34%) in the no screening group had died of ovarian cancer. The primary analysis using a Cox proportional hazards model gave a mortality reduction over years 0-14 of 15% (95% CI -3 to 30; p=0.10) with MMS and 11% (-7 to 27; p=0.21) with USS. The Royston-Parmar flexible parametric model showed that in the MMS group, this mortality effect was made up of 8% (-20 to 31) in years 0-7 and 23% (1-46) in years 7-14, and in the USS group, of 2% (-27 to 26) in years 0-7 and 21% (-2 to 42) in years 7-14. A prespecified analysis of death from ovarian cancer of MMS versus no screening with exclusion of prevalent cases showed significantly different death rates (p=0.021), with an overall average mortality reduction of 20% (-2 to 40) and a reduction of 8% (-27 to 43) in years 0-7 and 28% (-3 to 49) in years 7-14 in favour of MMS.	3

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
24. Menon U, Gentry-Maharaj A, Hallett R, et al. Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). Lancet Oncol. 2009; 10(4):327-340.	Experimental-Dx	202,638 post-menopausal women	Results of the prevalence (initial) screen of the UKCTOCS. Post-menopausal women were randomly assigned to no treatment (control; n=101,359); annual CA-125 screening (interpreted using a risk of ovarian cancer algorithm) with TVUS as a second-line test (multimodal screening; n=50,640); or annual screening with TVUS (US screening; n=50,639) alone in a 2:1:1 ratio using a computer-generated random number algorithm.	Sensitivity, specificity, and PPVs for all primary ovarian and tubal cancers were 89.4%, 99.8%, and 43.3% for multimodal screening, and 84.9%, 98.2%, and 5.3% for US screening, respectively. For primary invasive epithelial ovarian and tubal cancers, the sensitivity, specificity, and PPVs were 89.5%, 99.8%, and 35.1% for multimodal screening, and 75.0%, 98.2%, and 2.8% for US screening, respectively. Significant difference in specificity ($P<0.0001$) but not sensitivity between the two screening groups for both primary ovarian and tubal cancers as well as primary epithelial invasive ovarian and tubal cancers.	1
25. Menon U, Skates SJ, Lewis S, et al. Prospective study using the risk of ovarian cancer algorithm to screen for ovarian cancer. J Clin Oncol. 2005; 23(31):7919-7926.	Experimental-Dx	13,582 women recruited	To evaluate prevalence screening in the first prospective trial of a new ovarian cancer screening strategy (risk of ovarian cancer or ROC algorithm) on the basis of age and CA 125 profile.	Of 6,682 women randomly assigned to screening, 6,532 women underwent the first screen. After the initial CA 125, 5,213 women were classified as normal risk, 91 women elevated, and 1,228 women intermediate. On repeat CA 125 testing of the latter, a further 53 women were classified as elevated risk. All 144 women with elevated risk had TVUS. Sixteen women underwent surgery. Eleven women had benign pathology; one woman had ovarian recurrence of breast cancer; one woman had borderline; and three women had primary invasive epithelial ovarian cancer. The specificity and PPV for primary invasive epithelial ovarian cancer were 99.8% (95% CI, 99.7 to 99.9) and 19% (95% CI, 4.1 to 45.6), respectively. An ovarian cancer screening strategy using the ROC algorithm is feasible and can achieve high specificity and PPV in postmenopausal women.	1

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26. Kinkel K, Lu Y, Mehdizade A, Pelte MF, Hricak H. Indeterminate ovarian mass at US: incremental value of second imaging test for characterization--meta-analysis and Bayesian analysis. Radiology. 2005;236(1):85-94.	Meta-analysis	83 articles	To compare value of current diagnostic strategies in assessment of changes in posttest probability of ovarian cancer when menopausal status and combination and sequence of diagnostic imaging tests are considered.	Prevalence of ovarian cancer was 8.75% in premenopausal women and 32.40% in postmenopausal women with an ovarian mass. After characterization with initial gray-scale US, posttest probability in pre- and postmenopausal women changed, respectively, to 25% and 63% for indeterminate results and to 2% and 7% for benign results. Subsequent use of combined gray-scale and Doppler US, CT, or MR imaging had significant higher positive and lower negative posttest probability than did use of gray-scale US alone. In women with an indeterminate initial US result, posttest probability decreased after secondary testing with benign results for all imaging modalities to 2% in premenopausal women and to 8%-10% in postmenopausal women. After secondary testing for suspicious lesions, posttest probability increased more after non-enhanced (premenopausal women, 70%; postmenopausal women, 92%) or contrast-enhanced MR imaging (premenopausal women, 80%; postmenopausal women, 95%) than it did after combined gray-scale and Doppler US (premenopausal women, 30%; postmenopausal women, 69%) or CT (premenopausal women, 38%; postmenopausal women, 76%) ($P < .001$).	M

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27. Pickhardt PJ, Hanson ME. Incidental adnexal masses detected at low-dose unenhanced CT in asymptomatic women age 50 and older: implications for clinical management and ovarian cancer screening. Radiology. 2010;257(1):144-150.	Review/Other-Dx	2869 women	To determine the prevalence, work-up, and outcomes of indeterminate adnexal masses identified at low-dose unenhanced computed tomography (CT) in asymptomatic women age 50 and older undergoing colonography screening.	One hundred eighteen women (mean age, 56.2 years), representing 4.1% of the screening cohort, had an indeterminate adnexal mass (108 unilateral, 10 bilateral; mean size, 4.1 cm) at prospective CT interpretation. A total of 80 women underwent some combination of further imaging evaluation (n = 76) (transvaginal ultrasonography [n = 71], pelvic magnetic resonance imaging [n = 7], contrast material-enhanced CT [n = 7]) and/or surgery (n = 26). Mean serum CA-125 level in 33 women was 12.8 U/mL; levels were normal (<35 U/mL) in 32 (97%) cases (range, 3-26 U/mL) and mildly elevated (41 U/mL) in one case. Final pathologic findings of surgically excised lesions were cystadenoma or cystadenofibroma (n = 14; 11 serous, three mucinous); nonneoplastic cysts (n = 5; two endometriomas); mature teratoma (n = 3); hydrosalpinx (n = 2); fibroma (n = 1); and benign Brenner tumor (n = 1). Three additional teratomas were diagnosed at index CT only. No ovarian cancers were prospectively identified, although four cases of ovarian cancer developed subsequent to a negative adnexal finding at CT examination during a 15-44-month interval among the remaining 2751 women.	4

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28. Dodge JE, Covens AL, Lacchetti C, et al. Preoperative identification of a suspicious adnexal mass: a systematic review and meta-analysis. Gynecol Oncol. 2012;126(1):157-166.	Meta-analysis	57 articles	To systematically review the existing literature in order to determine the optimal strategy for preoperative identification of the adnexal mass suspicious for ovarian cancer.	Four meta-analyses and 53 primary studies were included in this review. The diagnostic performance of each technology was compared and contrasted based on the summary data on sensitivity and specificity obtained from the meta-analysis. Results suggest that 3D ultrasonography has both a higher sensitivity and specificity when compared to 2D ultrasound. Established morphological scoring systems also performed with respectable sensitivity and specificity, each with equivalent diagnostic competence. Explicit scoring systems did not perform as well as other diagnostic testing methods. Assessment of an adnexal mass by colour Doppler technology was neither as sensitive nor as specific as simple ultrasonography. Of the three imaging modalities considered, MRI appeared to perform the best, although results were not statistically different from CT. PET did not perform as well as either MRI or CT. The measurement of the CA-125 tumour marker appears to be less reliable than do other available assessment methods.	M
29. Gaarenstroom KN, van der Hiel B, Tollenaar RA, et al. Efficacy of screening women at high risk of hereditary ovarian cancer: results of an 11-year cohort study. Int J Gynecol Cancer. 2006; 16 Suppl 1:54-59.	Observational-Dx	269 women	Outcome of an 11-year cohort study on the value of screening women at high risk of hereditary ovarian cancer using TVUS and serum CA-125 testing.	113 (42%) of 269 women had a pathogenic BRCA1 or BRCA2 mutation, and 127 (47%) of 269 women had salpingo-oophorectomy. Malignancy was found in 8 women having both elevated CA-125 levels and abnormal US findings. 4 of these cancers (one borderline, one stage Ia, one stage IIIb, and one stage IIIc ovarian or peritoneal cancer) were detected at the first screening visit. One stage IIIb and one stage IIIc cancer were detected at the second screening visit after 12 months, and two interval stage IIIc and IV cancers were detected 8 and 10 months after the first screening visit.). Because most cancers were detected at an advanced stage, value of screening women at high risk of ovarian cancer seems poor.	3

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
30. Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. J Clin Oncol. 2004; 22(7):1315-1327.	Review/Other-Dx	N/A	To analyze the clinicopathologic features of screen-detected ovarian cancers identified in women, either at general population risk or high genetic risk of ovarian cancer, who have participated in screening studies.	Of the stage I tumors detected by screening women at population risk, almost half were borderline ovarian tumors, granulosa-cell tumors, or germ-cell tumors, which is disproportionate to their frequency. Furthermore, of the stage I invasive epithelial cancers diagnosed in women at population risk, the majority were endometrioid, clear-cell, and mucinous histologic subtypes. Most ovarian cancers that occur in women at high genetic risk are high-grade serous cancers, and these are infrequently screen detected at an early stage. The clinicopathologic features of screen-detected ovarian cancers suggest that screening may not reduce mortality in women at increased genetic risk. Prospective screening studies are required in genetically high-risk populations to answer this important question. Women electing surveillance should be aware of the lack of proven benefit and the low likelihood of detecting early stage serous cancers. Bilateral salpingo-oophorectomy appears to be the most effective approach to decrease the risk of ovarian cancer and thereby reduce mortality in high-risk women.	4

Ovarian Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
31. Olivier RI, Lubsen-Brandsma MA, Verhoef S, van Beurden M. CA125 and transvaginal ultrasound monitoring in high-risk women cannot prevent the diagnosis of advanced ovarian cancer. Gynecol Oncol. 2006; 100(1):20-26.	Observational-Dx	312 women	To evaluate ovarian cancer screening by means of pelvic examination, serum CA 125 and TVUS in a consecutive series of high-risk women.	Among 10 women with an elevated CA 125 level and a positive TVUS, 3 screening carcinomas (one FIGO stage IC, one stage IIIB and one stage IV) and one interval carcinoma (stage IV) were detected. Five occult ovarian/fallopian tube carcinomas (two stage IA, one stage IC, one stage IIIB and one stage IV) after bilateral prophylactic (salpingo-) oophorectomy have been found in 152 women. The sensitivity, specificity, PPV and NPV of the combination of CA 125 and TVUS were the highest (40%, 99%, 40% and 99%) followed by CA 125 alone (50%, 96%, 13% and 99%), pelvic exam (40%, 98%, 21% and 99%) and TVUS, separately (40%, 90%, 6% and 99%). By combining CA 125 with TVUS results, a PPV of 40% was achieved. However, the diagnostic tools appear to be only sensitive in detecting ovarian cancer at an advanced stage, while three of four tumors with early-stage disease in this series had normal screening tests prior to the diagnosis.	3
32. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? Int J Cancer. 2009; 124(4):919-923.	Observational-Dx	241 consecutive women	To determine the effectiveness of ovarian cancer screening in women with a BRCA1/2 mutation.	3 ovarian cancers were detected during the surveillance period; 1 prevalent cancer, 1 interval cancer and 1 screen-detected cancer, all in an advanced stage (FIGO stage IIIc). A PPV of 20% was achieved for pelvic examination, 33% for TVUS and 6% for CA 125 estimation alone. The NPV were 99.4% for pelvic examination, 99.5% for TVUS and 99.4% for CA 125. All detected ovarian cancers were in an advanced stage, and sensitivities and PPVs of the screening modalities are low. Restricting the analyses to incident contacts that contained all 3 screening modalities did not substantially change the outcomes. Annual gynecological screening of women with a BRCA1/2 mutation to prevent advanced stage ovarian cancer is not effective.	3

Ovarian Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
33. Stirling D, Evans DG, Pichert G, et al. Screening for familial ovarian cancer: failure of current protocols to detect ovarian cancer at an early stage according to the international Federation of gynecology and obstetrics system. J Clin Oncol. 2005;23(24):5588-5596.	Observational-Dx	1110 women	To assess the effectiveness of annual ovarian cancer screening (transvaginal ultrasound and serum CA-125 estimation) in detecting presymptomatic ovarian cancer in women at increased genetic risk.	Thirteen epithelial ovarian malignancies (12 invasive and one borderline), developed in the cohort. Ten tumors were detected at screening: three International Federation of Gynecology and Obstetrics (FIGO) stage I (including borderline), two stage II, four stage III, and one stage IV. Of the three cancers not detected by screening, two were stage III and one was stage IV; 29 women underwent diagnostic surgery but were found not to have ovarian cancer. Annual surveillance by transvaginal ultrasound scanning and serum CA-125 measurement in women at increased familial risk of ovarian cancer is ineffective in detecting tumors at a sufficiently early stage to influence prognosis. With a positive predictive value of 17% and a sensitivity of less than 50%, the performance of ultrasound does not satisfy the WHO screening standards. In addition, the combined protocol has a particularly high false-positive rate in premenopausal women, leading to unnecessary surgical intervention.	3
34. Rosenthal AN, Fraser L, Manchanda R, et al. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol. 2013;31(1):49-57.	Observational-Dx	3,563 women	To establish the performance characteristics of annual transvaginal ultrasound and serum CA125 screening for women at high risk of ovarian/fallopian tube cancer (OC/FTC) and to investigate the impact of delayed screening interval and surgical intervention.	Sensitivity for detection of incident OC/FTC at 1 year after last annual screen was 81.3% (95% CI, 54.3% to 96.0%) if occult cancers were classified as false negatives and 87.5% (95% CI, 61.7% to 98.5%) if they were classified as true positives. Positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100) respectively. Four (30.8%) of 13 incident screen-detected OC/FTCs were stage I or II. Compared with women screened in the year before diagnosis, those not screened in the year before diagnosis were more likely to have >/= stage IIIc disease (85.7% v 26.1%; P = .009). Screening interval was delayed by a median of 88 days before detection of incident OC/FTC. Median interval from detection screen to surgical intervention was 79 days in prevalent and incident OC/FTC.	3

Ovarian Cancer Screening
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
35. Lacey JV, Jr., Greene MH, Buys SS, et al. Ovarian cancer screening in women with a family history of breast or ovarian cancer. Obstet Gynecol. 2006; 108(5):1176-1184.	Experimental-Dx	28,460 women	To evaluate PPVs of CA 125 or TVUS screening for ovarian cancer according to family history of breast or ovarian cancer.	Similar proportions (4.8%-5.0%) of women in each group had abnormal screening results. Higher-risk women were more likely than lower-risk women to undergo biopsy after a positive screen. Screening identified 43 invasive ovarian cancers. The PPVs for abnormal screening results were 0.7% in average-risk, 1.3% in moderate-risk, and 1.6% in high-risk groups; one ovarian cancer occurred among the breast cancer survivors. The PPVs for postbaseline abnormal screening results were also higher in the higher-risk groups. The PPVs did not significantly differ across risk groups. Probabilities of abnormal annual CA 125 and TVUS screens were similar across groups based on family history of breast or ovarian cancer. However, ovarian cancer was more likely to be diagnosed after an abnormal screening result among women at higher family history-based risk than among women at lower risk.	1
36. Lai T, Kessel B, Ahn HJ, Terada KY. Ovarian cancer screening in menopausal females with a family history of breast or ovarian cancer. J Gynecol Oncol. 2016;27(4):e41.	Observational-Dx	78216 women	To determine whether annual screening reduces ovarian cancer mortality in women with a family history of breast or ovarian cancer.	There was no significant difference in overall mortality or disease specific mortality between the two arms. Ovarian cancer was diagnosed in 48 patients in the screening arm and 44 patients in the usual care arm. Screened patients were more likely to be diagnosed at an earlier stage than usual care patients. Patients in the screening arm diagnosed with ovarian cancer experienced a significantly improved survival compared to patients in the usual care arm; relative risk 0.66 (95% CI, 0.47 to 0.93).	3
37. American College of Radiology. ACR Appropriateness Criteria® Radiation Dose Assessment Introduction. Available at: http://www.acr.org/~/media/ACR/Documents/AppCriteria/RadiationDoseAssessmentIntro.pdf.	Review/Other-Dx	N/A	Guidance document on exposure of patients to ionizing radiation.	N/A	4

Evidence Table Key

Study Quality Category Definitions

- *Category 1*: The study is well-designed and accounts for common biases.
- *Category 2*: The study is moderately well-designed and accounts for most common biases.
- *Category 3*: There are important study design limitations.
- *Category 4*: The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.
- M = Meta-analysis

Dx = Diagnostic

Tx = Treatment