Ultrasound follow up of an adnexal mass has the potential to save lives

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A recent retrospective research article "Outcomes from Ultrasound Follow-up of Small Complex Adnexal Mass in Women over 50"[1] states that repeated monitoring of a stable but persistent indeterminant lesion according to the Society of Radiologists in Ultrasound (SRU) Guideline[2] is of questionable benefit based on the "fact that (1) no benefit has ever been demonstrated from long-term monitoring, (2) stability over time argues strongly against malignancy, (3) benign lesions are not generally precursors of malignant lesions, and (4) indefinitely repeated ultrasound monitoring exposes women to many of the same risks that are seen with ovarian cancer screening and as such may actually result in harm." These authors state that monitoring adnexal masses beyond 7 months for the purpose of excluding malignant cause is of limited use. Our review of the literature shows otherwise. It should be noted that both the retrospective analysis by Suh-Burgmann et al[1] and expert views from the SRU consensus conference[2] are subject to different, as well as overlapping, levels of uncertainty.

A systemic literature review was conducted with the use of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) criteria to evaluate the quality of evidence, assess the key areas of uncertainty, and summarize the balance of benefits and harms of specific recommendations. The review criteria consisted of 88 PubMed searches that were conducted by a research librarian, of which 23 were used to focus findings that were based on various Boolean sorts (Literature search terms included *((((adnex* AND (ULTRASON* OR ULTRASOU*) AND (OUTCOME* OR RESULT* OR PROGNOS*))) OR (((((((("Adnexa Uteri"[Majr]) OR "Adnexal Diseases"[Majr])) AND ((("ultrasonography" [Subheading]) OR "Ultrasonography"[Mesh]))) OR ((((("Adnexal Diseases/ultrasonography"[Majr]) OR "Adnexa Uteri/ultrasonography"[Majr]))))) AND "Prognosis"[Mesh]))) AND "Genital Neoplasms, Female/ultrasonography"[Majr] Filters: Humans; English; Middle Aged + Aged: 45+ years*. Results before the year 2000 and any from nonrefereed journals were excluded. This yielded a total of 169 articles; quality was assessed with the use of a modified version of the Quality Assessment of Diagnostic Accuracy Studies assessment tool. Further review of the 169 articles for relevance for the prediction of ovarian malignancy based on ultrasound scans yielded 30 articles. The final aim of the search was to identify those original articles in which an ovarian mass that had been found by ultrasound scanning was evaluated for a risk of ovarian cancer. Articles were excluded if they were (1) letters to the editors, (2) case reports, or (3) duplicate reports from the same authors' group. The significant reports referenced here are summarized with the use of GRADE (Figure 1).

Serial ultrasound scanning leads to an improved positive predictive value for ovarian malignancy[3] and a shift to detection at earlier stages.[3-5] Malignancy has been found in apparently stable masses that eventually enlarged and increased in morphologic complexity in up to 3 years after initial detection.[6] These results gleaned from 11,982 ultrasound examinations define the risks from terminating ultrasound surveillance.[6] We have used the definition of acceptable risk level from environmental studies of no more than 1 extra death per 100,000 deaths to normalize the reported data.[7] The absolute risks calculated from the United Kingdom Collaborative Trial of Ovarian Cancer Screening trial data for the appearance of malignancy in up to 3 years after an initial ultrasound examination are considerably elevated (Figure 2).[6] As judged by the 95% confidence intervals, the risk of malignancy is higher in any of the ovarian ultrasound abnormalities (Figure 2). Allowing for a 10-fold relaxation of the 0.001% acceptable risk level would still predict a considerable number of extra malignancies within 3 years of the first scan. If ≥50% of these malignancies were diagnosed as advanced stage that are destined to be fatal, then the expectation for extra deaths because of curtailing surveillance is high and identifies the peril of limiting ultrasound surveillance. It is our opinion that continuing surveillance with serial ultrasound scans provides protection against these risks, while reducing the accrual of false-positives and the related unnecessary benign surgeries[3] that would result if indeterminate masses that are destined to resolve are surgically removed rather than monitored.

The current concept of ovarian cancer ontogeny is that type-1 tumors go through stepwise progression from benign cystadenomas to borderline tumors and invasive epithelial cancers.[8-10] This progression is analogous to the adenoma-to-carcinoma sequence seen in colorectal carcinoma pathogenesis or the hyperplasia-to-carcinoma sequence in endometrioid carcinoma of the endometrium.[9] Just as endometriosis, a

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Received March 25, 2015; revised June 15, 2015; accepted June 16, 2015.

The authors report no conflict of interest.

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0002-9378/$36.00 •
http://dx.doi.org/10.1016/j.ajog.2015.06.041

FIGURE 1

Summary of significant reports

Comparison	Outcome	Study design	Findings	Evidence	Reference #
TVS screen vs no screen for ovarian cancer	Early stage detection and survival benefit	Prospective Population Control	Early ovarian cancer stage detection, survival benefit, resolution of benign abnormality on serial follow up	Level 1	3, 16, 22, 25
TVS screen vs no screen for ovarian cancer	Early stage detection	Randomized Prospective Control Trial	Early stage detection. Survival benefit yet to be published.	Level 1	4, 5, 6
BRCA 1 and 2 carriers with prophylactic bilateral oophorectomy vs nonsurgery in evaluating incidence of ovarian and breast cancer.	Advocate prophylactic oophorectomy to reduce the risk of ovarian and breast cancer in women with *BRCA1* or *BRCA2* mutations.	Randomized Prospective Control Trial	Bilateral prophylactic oophorectomy reduces the risk of coelomic epithelial cancer and breast cancer in women with *BRCA1* or *BRCA2* mutations.	Level 1	23
Endometrioid ovarian carcinoma versus endometriosis	Recommendation that ovarian endometrioma in post menopausal women should be removed when detected.	Systemic review and retrospective cohort	More postmenopausal women had concurrent endometriosis and endometrial cancer. Transition site from benign to malignant epithelium was observed. Endometriosis was present only in patients with Grade 1 or Grade 2 carcinomas.	Level 2	11
Benign to malignant transition in serous and mucinous ovarian cystadenocarcinoma	Recommendation that removal of benign serous and mucinous ovarian tumors should result in subsequent reduction in frequency of ovarian cancer.	Systemic review and retrospective cohort	Benign epithelium adjacent to an area of borderline or malignant epithelium was observed in 79% of serous and mucinous ovarian cystadeoncarcinomas. A site of epithelial transition was noted in 40% of cases. The presence of associated benign epithelium was more common in borderline or well-differentiated lesions and in patients with early-stage disease.	Level 2	12
Benign to malignant transformation of mature cystic teratoma of ovary.	Recommendation that early detection of malignant transoformation improves survial.	Systemic review of retrospective cohort	Malignant transformation is rare however it tends to occur in older women, larger tumor size and mass with solid component.	Level 2	14
Symptoms of ovarian cancer patient and control subjects.	Recommend cautious approach to use of symptoms to trigger extensive evaluation. Large scale implementation of this approach is premature.	Case control	Difference in symptoms between the two groups yielded very low positive predictive value. The prevalence of invasive ovarian cancer was ten times higher than that reported in screening studies.	Level 2	17, 18
Growth pattern among small adnexal masses described as "complex" in radiology report in nonstandarized reporting system.	Recommendation that all "small" adnexal masses beyond 7 months is of limited use.	Retrospective case series	Small adnexal masses less than 6 cm that were described as "complex" by some radiologists did not grow in size beyond 7 months. The study excludes all other consecutive adnexal masses that did not contained "complex" in nonstandarized reporting, therefore evaluating effectiveness of the term "complex" is how the patients were managed.	Level 3	1
Survival and cost of managing stage 3c epithelial ovarian cancer	Observation that long term disease free survival is low and financial cost of treatment is significant.	Non-experimental study	Patient survival was 30% at 5 years and only 9% of patients disease free > 5 years after treatment. The average cost of treatment was $211,940 per patient.	Level 3	19
Guideline	Evidence based practice Guideline	Expert consensus panel and review	Management of benign and indeterminate masses. Benign masses such as simple cyst on ultrasound should not have follow-up.	Level 4	2, 15
Guideline	Recommendation	Expert consensus panel	Environmental monitoring	Level 5	7
Literature Review	Summary of recent research on types of ovarian cancer.	Literature review	Type 1 and Type 2 ovarian cancers have different pathogenesis and progression.	Level 5	8, 9, 10