False Positives Induced by Annual Screening US Added to Mammography: ACRIN* 6666
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Purpose: To investigate rates of recall, biopsy, and short interval follow-up and rates of malignancy for each, when annual screening ultrasound (US) is added to mammography in women at elevated risk of breast cancer.

Methods: 2809 women at elevated risk for breast cancer with nonfatty breasts were recruited 4/04 to 2/06 from 21 IRB-approved sites to undergo mammography (M) and physician-performed US exams, randomized in order, masked, and interpreted by different physicians prior to integrated interpretation, with screening at time 0 (year 1), 12 (year 2), and 24 months (year 3). Reference standard is based on biopsy and/or 12-month follow-up for each screen. PPV1 (cancers/cases recalled for additional imaging) and PPV2 (cancers/biopsies recommended after workup) were calculated.

Results: 2648 participants had reference standard for year 1; 2487 for year 2; and 1921 for year 3. In year 1, 20 cancers were identified on M and 31 after M+US, with PPV1 = 7.2% (20/279) for M and 6.9% (31/448) for M+US and PPV2 = 22% (19/87) for M and 10.7% (31/289) for M+US. In year 2, 16 cancers were identified on M and 25 after M+US, with PPV1 = 6.2% (16/260) for M and 6.7% (25/373) for M+US and PPV2 = 25% (15/61) for M and 13.0% (24/184) for M+US. One cancer was followed or dismissed in each of years 1 and 2 after workup. In year 3, 23 cancers were identified on M and 31 after M+US, with PPV1 = 13.1% (23/175) for M and 11.5% (31/270) for M+US and PPV2 = 40% (23/57) for M and 19.5% (31/159) for M+US. Short interval follow-up was recommended as follows: year 1, 109/2648 (4.1%) on M and 336 (12.7%) after M+US; year 2, 59/2487 (2.4%) on M and 139 (5.6%) after M+US; and year 3, 29/1921 (1.5%) on M and 87 (4.5%) after M+US. Of 197 participants recommended for short-interval follow-up on M, 1 (0.5%) was diagnosed with cancer before the next screen, compared to 4/562 (0.7%) after M+US.

Conclusions: Annual US resulted in additional biopsy recommendation in 225/4408 (5.1%) screens in years 2 and 3 and only 17/225 (7.6%) proved to have cancer; PPV1 and PPV2 of M+US did increase in year 3 compared to the prevalence screen. Additional short-interval follow-up was prompted in 138/4408 (3.1%) incidence screens based on US.

Clinical Relevance/Application: False positive biopsies remain problematic for screening US even on subsequent screening rounds. Rates of short interval follow-up prompted by US decreased on incidence vs. prevalence screens.