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MAKING SENSE OF THE MAMMOGRAPHY DEBATE: A METHODS TUTORIAL

In November, 2009, the U.S. Preventive Services Task Force (USPSTF) updated recommendations for breast cancer screening. The new guidelines, based on updated review of the evidence, recommend against routine screening mammography for women aged 40-49 in the general population, call for biennial screening mammography in women aged 50-74, and state that the evidence is insufficient to recommend continued screening after age 75.¹ These new recommendations have been the subject of heated debate, especially focused on the subset of women aged 40-49. This tutorial is intended to help readers better understand and communicate with women about the underlying scientific issues.

Screening tests asymptomatic people at risk for a disease, with the goal of early detection, effective prevention or treatment, and improved outcomes. To be beneficial, screening for cancer must identify the disease earlier, and lead to treatment with better outcomes than treatment starting at the onset of disease symptoms without screening; benefits of screening must also outweigh harms of screening.² Characteristics of both the test and the disease affect the value of a screening test. Test characteristics include sensitivity and specificity. Sensitivity is the ability of mammography to correctly identify those with the disease, while specificity is the ability of mammography to correctly rule out the disease in those who do not have it. Specificity is especially important in population-based breast cancer screening regimens because of significant harms, both physical and psychological, and costs, associated with follow-up for a positive screening test.³ Disease characteristics that affect screening performance include the prevalence of the condition and its natural history, i.e., whether and how fast it tends to progress, whether it may resolve spontaneously, and how it affects survival. These factors must be weighed against the potential harms of screening, which can include loss of perceived health, harms and costs of further testing to refute false positive test results, and harms and costs of overdiagnosis and pseudo-cure—unnecessary treatment because the disease

found would not have affected the person had it remained unidentified.

In two decades of population-based mammography screening programs, the incidence of breast cancer has risen reflecting earlier detection, especially of localized, early-stage cancers that may represent lower risk to survival. However, data suggest that screening has not significantly reduced the burden of aggressive fast-growing cancers, and thus has not resulted in the expected reduction in overall mortality. Ductal carcinoma in situ and some small tumors might never put a woman's life at risk; however, because natural disease progression is poorly understood, once detected they are routinely treated, entailing harm and cost with uncertain benefit. Conversely, routine population screening likely misses many aggressive cancers in younger women. Thus, it may be incorrect to assume that finding and treating early-stage cancer will prevent late-stage, metastatic disease.⁴ Moreover, a recent model estimating the absolute benefit of screening mammography concluded that less than 5% of women with screening-detectable breast cancers had their life saved by the test.⁵

The risk of breast cancer increases with age, increasing the positive predictive value of tests for older women. But breast cancer is not a homogeneous disease; most breast cancers are slow-growing, and undetected some may resolve spontaneously.⁶ Thus, knowing about a disease earlier is not always beneficial, but can increase risk of harms from unnecessary follow-up diagnostic tests and treatment. A recent systematic review of population mammography screening programs estimated that one in three breast cancers is overdiagnosed.⁷

Modeling of effects of various mammography screening schedules using national data from cancer registries suggested that the most efficient regimen for reducing mortality entails biennial screening starting at age 50, while biennial screening starting at age 40 would be expected to maximize life-years gained assuming tolerance for harms associated with false positives and overdiagnosis.⁸ Most reports of effects of treatments give greater prominence to benefits than harms, and poorly reflect the trade-offs between harms and benefits.⁹ The current USPSTF screening guidelines attempt to account for significant harms associated with population-based screening of women under age 50 and over age 75, while maximizing benefits of screening across the population of U.S.

women of average risk. As under any population-based guideline, screening decisions for individual women should take into consideration their specific risk profile.

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FROM COCHRANE DATABASE OF SYSTEMATIC REVIEWS (CDSR), ISSUE 4, 2009

New Systematic Reviews

- Fundal pressure during the second stage of labour
- Interventions for preventing unintended pregnancies among adolescents
- Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen
- Medical treatments for idiopathic thrombocytopenia purpura during pregnancy
- Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women
- Post-embryo transfer interventions for in vitro fertilization and intracytoplasmic sperm injection patients

- Probiotics for the treatment of bacterial vaginosis
- Routine pre-pregnancy health promotion for improving pregnancy outcomes

Updated Systematic Reviews

- Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery
- Antibiotics for gonorrhoea in pregnancy
- Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants
- Effects and safety of preventive oral iron or iron+folic acid supplementation for women during pregnancy
- Hydration for treatment of preterm labour
- Induction of labour for suspected fetal macrosomia
- Intrapartum interventions for preventing shoulder dystocia
- Intravenous oxytocin alone for cervical ripening and induction of labour
- Operative versus conservative management for ‘fetal distress’ in labour
- Oral contraceptive pill for heavy menstrual bleeding
- Screening for breast cancer with mammography

Cochrane Reviews are available by subscription to *The Cochrane Library*, and review abstracts are available without charge. See <http://www.cochrane.org/reviews/>

FROM DATABASE OF ABSTRACTS OF REVIEWS OF EFFECTS (DARE)

Recent Abstract Entries Assessing Quality of Systematic Reviews

- Aromatase inhibitors in adjuvant therapy for hormone positive breast cancer: A systematic review
- Cervical stitch (cerclage) for preventing pregnancy loss: Individual patient data meta-analysis
- Clinical decision support tools for osteoporosis disease management: A systematic review of randomized controlled trials
- Do perineal exercises during pregnancy prevent the development of urinary incontinence: A systematic review
- Effects of treating postnatal depression on mother-infant interaction and child development: Systematic review
- Induction of labor versus expectant management for post-date pregnancy: Is there sufficient evidence for a change in clinical practice?
- Meta-analysis of intrauterine device use and risk of endometrial cancer
- Preventing postpartum depression part I: A review of biological interventions
- Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis
- The effectiveness of HIV partner counseling and referral services in increasing identification of HIV-positive individuals: A systematic review

- Use of antibiotics for the treatment of preterm parturition and prevention of neonatal morbidity: A meta-analysis

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EVIDENCE-BASED REVIEWS FROM OTHER SOURCES

Featured review: Hutton EK, Kasperink M, Rutten M, Reitsma A, Wainman B. Sterile water injection for labour pain: A systematic review and meta-analysis of randomised controlled trials. BJOG 2009;116, 1158-66.

A systematic review and meta-analysis of 8 randomized controlled trials explored whether receiving sterile water injections had an effect on risk of cesarean delivery in women with low back pain during active labor who requested pain relief other than regional anesthesia. Cesarean section rates were compared in women with back pain in labor randomized to receive sterile water injections, placebo, or an alternative non-pharmacological pain management technique, such as transcutaneous electric nerve stimulation (TENS) or acupuncture. Other outcomes were self-reported pain relief measured by the visual assessment scale (VAS), and subsequent use of regional anesthesia. The relative risk of cesarean delivery in the sterile water injection group was near half that of the comparison group (RR 0.51, 95% CI: 0.30-0.87, $p = 0.01$). There was no significant difference in baseline pain on the VAS or in subsequent use of regional anesthesia between the two groups. Women receiving sterile water injections reported significantly lower pain scores at 10-30 minutes, 45-60 minutes, and 90-120 minutes. Sixty-nine percent of women receiving the treatment indicated they would be willing to have it again.

Comment: Up to a third of women experience added pain from back labor while giving birth. A low-technology, low-cost technique that is acceptable to women, has no known downsides, and can halve the rate of cesarean delivery in this population has important implications for practice.

Featured review: Renfrew MJ, Craig D, Dyson L, McCormick F, Rice S, King SE, et al. Breastfeeding promotion for infants in neonatal units: A systematic review and economic analysis. NIHR HTA 2009;13, 40. Available at: <http://www.hta.ac.uk/1611>

The authors undertook a systematic review and economic evaluation to assess effectiveness and cost-effectiveness of interventions aimed at promoting breastfeeding among infants in neonatal intensive care units. For all 48 studies included, eligibility criteria were applied and study quality was assessed; pooled data analysis was undertaken whenever possible. The strength of the conclusions was limited by the number and quality of studies evaluating specific interventions; no studies met the selection criteria for the planned economic review. Studies were limited to

clinically stable infants. Several interventions showed promise based on data from multiple high to moderate quality studies. The reviewers found strong evidence to suggest that even short periods of skin-to-skin mother-baby contact are associated with increased duration of breastfeeding. Peer support programs, both home- and hospital-based, demonstrated effectiveness in increasing breastfeeding duration. Simultaneously pumping both breasts with an electric pump was associated with increased milk expression per feed in the first two weeks postpartum. Limited evidence suggested a benefit from cup feeding compared to bottle feeding in decreasing oxygen desaturation during feeding and increasing the rate of breastfeeding at discharge. Staff training was associated with improved initiation and duration of breastfeeding, also based on limited evidence. Multi-faceted system-level interventions were effective at improving various breastfeeding outcome measures, as observed in studies of the effects of implementing the UNICEF Baby Friendly Hospital Initiative.

Comment: The benefits associated with breastfeeding, including reduced rates of infections and decreased incidence of necrotizing enterocolitis, are particularly important in the fragile population of infants in special care units. With US rates of preterm birth and low birthweight that have risen steadily over the last two decades, effective interventions are needed to promote this health enhancing and lifesaving practice.

Featured review: Terplan M, Smith EJ, Temkin SM. Race in ovarian treatment and survival: A systematic review with meta-analysis. Cancer Causes Control 2009;20, 1139-50.

A systematic review with meta-analysis was conducted to assess whether race is an independent predictor of ovarian cancer treatment and outcomes in the United States. The authors looked for evidence of the existence and effects of unequal treatment of ovarian cancer between black and white women. Twenty-four studies conducted through 2008 were included that examined treatment, survival, or both by race. Study data were pooled when appropriate. Currently recommended treatment for ovarian cancer consists of aggressive surgical debulking of the tumor burden followed by platinum-based chemotherapy. A meta-analysis of 8 studies indicated that white women were 17% more likely to receive surgical treatment, and 20% more likely to have both surgery and chemotherapy than their black study counterparts. Pooled analysis of data from 106,704 women showed no statistically significant difference in five-year survival by race. However, an interesting finding emerged when the study data were stratified by diagnosis either before or after the emergence of the treatment protocol described above, which has been shown to extend survival. White women had significantly poorer survival rates than black women prior to 1985 when no effective treatment existed, but significantly better odds of

survival after that cut-point. Furthermore, the disparity in survival by race is similar in magnitude to the disparity in the chances of receiving the gold standard treatment during the same period.

Comment: It is difficult to separate evidence of unequal treatment from possible underlying differences in biologic risk and to control for confounders. However, the present study makes a compelling case that disparities in the treatment of black women with ovarian cancer are associated with poorer outcomes compared to white women with this disease, given data demonstrating better odds of survival for black women prior to the emergence of the current gold standard for treatment.

Recent Evidence-Based Reviews

- Caughey AB, Sundaram V, Kaimal AJ, Gienger A, Cheng YW, McDonald KM. Systematic review: Elective induction of labor versus expectant management of pregnancy. *Ann Int Med* 2009;151, 252-63.
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