International Journal of Technology Assessment in Health Care, **17:3** (2001), 275–304.

THE ACCURACY AND EFFECTIVENESS OF ROUTINE POPULATION SCREENING WITH MAMMOGRAPHY, PROSTATE-SPECIFIC ANTIGEN, AND PRENATAL ULTRASOUND

*A Review of Published Scientific Evidence**

Steven H. Woolf
Virginia Commonwealth University

Abstract

Objective: To review published data regarding the accuracy and effectiveness of three screening tests: mammography, prostate-specific antigen (PSA), and prenatal ultrasound.
Methods: Published evidence regarding the accuracy and effectiveness of the three tests was collected by computerized literature search and supplemented by manual review of relevant bibliographies.
Results: Screening mammograms lower breast cancer mortality by about 20%. Most data come from women aged 50–64 years; women aged 40–49 years may also benefit, but the absolute risk reduction is lower. Up to 1,500 to 2,500 women must undergo screening to prevent one death from breast cancer. Mammograms miss approximately 12% to 37% of cancers, generate false-positive results, and cause anxiety while abnormal results are evaluated. PSA screening can detect 80% to 85% of prostate cancers but has a high false-positive rate. There is little direct evidence that early detection reduces morbidity or mortality. Indirect evidence includes a trend toward earlier stage tumors and steadily declining mortality rates in geographic areas where PSA screening has become common. Potential harms include the morbidity associated with evaluating abnormal results, and complications from treatment (e.g., impotence, incontinence). The overall balance of benefits and harms remains uncertain in the absence of better evidence. Prenatal ultrasound may reduce perinatal mortality, primarily through elective abortions for congenital anomalies, but does not appear to lower live birth rates. Although ultrasound has no proven effect on neonatal morbidity, it provides more accurate estimates of gestational age that prevent unnecessary inductions for post-term pregnancy. Screening detects multiple gestations, congenital anomalies, and intrauterine growth retardation, but direct health benefits from having this knowledge are unproved. Ultrasound has both positive and negative psychological effects on parents. The scans do not appear to harm childhood development.
Conclusions: Even for the most established screening tests, the appropriateness of routine testing depends on subjective value judgments about the quality of supporting evidence and about the trade-offs between benefits and harms. Individuals, clinicians, policy makers, and governments must weigh the evidence in light of these values and the constraints imposed by available resources.

Keywords: Screening, Preventive medicine, Mammography, Prostate-specific antigen, Prenatal ultrasound

*This article was submitted for publication in June 2000 and has not been updated to reflect new evidence that has been published since that time.

A series of articles in this issue discuss the use of three screening tests in Europe: mammographic screening for breast cancer, measurement of prostate-specific antigen (PSA) to screen for prostate cancer, and prenatal ultrasound screening. As part of that project, this review was commissioned to provide a summary of the core international scientific evidence on which such screening efforts are based. The review was first performed in 1997 and was updated in 2000.

Resource limitations and space constraints preclude the author from publishing the full documentation that accompanies systematic reviews (56), but a comprehensive literature search and critical appraisal of approximately 250 relevant studies are provided here. The review deals only with secondary prevention, targeting asymptomatic people who have developed occult disease; it does not discuss testing of patients with clinically evident disease. The review also excludes primary prevention (e.g., dietary and lifestyle changes), which is potentially more effective than screening in lowering morbidity and mortality from the cancers and perinatal conditions discussed here.

The principal factors to consider in determining the appropriateness of population screening include: a) the burden of suffering from the target condition (e.g., incidence and prevalence of disease, mortality, morbidity, costs of care); b) the accuracy of the screening test (e.g., sensitivity, specificity) in detecting early-stage disease; c) the effectiveness of early detection in improving outcomes and the trade-off between benefits and potential harms; d) resource constraints (e.g., cost-effectiveness); e) the ability of clinicians, patients, and the healthcare system to implement a screening program (e.g., feasibility, acceptability, uptake, patient education, adherence, follow-up); f) philosophical and moral objections; and g) opportunity costs (e.g., if screening displaces resources needed for other, perhaps more effective, healthcare services).

This article reviews the evidence for only the second and third items (accuracy of screening tests and effectiveness of early detection). Other factors are critical to setting public policy but are not discussed here because they tend to be country-specific. It is often because of country-specific factors that a screening test with the same supporting evidence may be widely implemented in one country and not another. Individual countries face different priorities and values in determining whether and how to implement screening, and they operate under different healthcare systems, resource constraints, and organizational models for delivering screening (18).

Attitudes differ, for example, on whether a screening test with theoretical but unproved benefit (e.g., PSA) should be encouraged, about the ethical imperative to ensure that the potential harms of screening tests (e.g., labeling, testing for false-positive results) do not outweigh their putative benefits, and about the resources that such screening deserves. A principal argument for prenatal screening for congenital anomalies is to give women the option of terminating their pregnancy. Whether this option is legal and consistent with religious and ethical mores varies from country to country.

GENERAL PRINCIPLES

A screening test is considered accurate if it can detect a large proportion of persons with early-stage disease without generating a large number of false-positive results. In epidemiologic terms, the test must have good *sensitivity* (the proportion of persons with a disease who test positive) and *specificity* (the proportion of persons without a disease who test negative). Tests with poor sensitivity produce a greater proportion of false-negative results, allowing persons with the condition to escape detection. Tests with poor specificity produce a greater proportion of false-positive results, which may lead to unnecessary anxiety and follow-up tests. Sensitivity and specificity are often inversely related, so that setting a lower threshold

to detect more cases may improve sensitivity at the expense of specificity, increasing the frequency of false-positive results.

A common measure of the accuracy of a screening test is the positive predictive value (PPV), the probability of that the target condition is present if the test is positive. A PPV of 25% means that three of four abnormal test results will be falsely positive. The PPV of a screening test varies with the pretest probability of the condition. A PPV of 40% in a population with an increased risk of the disease, such as screening for breast cancer in women with an affected first-degree relative, is likely to be lower when screening is performed in the general population. PPV values cannot be generalized without considering local prevalence rates.

Accuracy, by itself, is an insufficient basis for screening. There must also be evidence that early detection is beneficial, that persons identified with early-stage disease through screening have better health outcomes than those who come to clinical attention without screening. Such evidence is best obtained from randomized controlled trials. Observational studies suggesting benefit for persons with early-stage disease are often less compelling because of concerns about selection bias, retrospective design, measurement error, confounding variables, and, often, the absence of an internal control group. Wherever possible, this review focuses on evidence available in randomized controlled trials, recognizing that evidence from other sources can be useful when such trials are unavailable.

Finally, the effectiveness of early detection cannot be fully assessed without considering potential harms. These include the direct effects of the screening procedure, which are usually minor, and those from false-negative and false-positive results. The former can give false reassurance about the absence of disease and may lead patients to ignore warning signs and symptoms. False-positive results can generate anxiety as patients undergo and await test results, and may have long-term labeling effects. Follow-up tests can cause complications, and some patients may undergo unnecessary treatment. This includes treatment of conditions that, although not falsely positive, are unlikely to affect the patient's future health (e.g., low-grade latent prostate cancer). Clinicians often feel compelled to treat such conditions if they pose a risk for future disease. Even when screening detects clinically significant disease, the adverse effects of treatment (e.g., drugs, surgery) may offset the benefits of early detection.

SCREENING MAMMOGRAPHY

Radiographic breast imaging is one of several means of detecting early-stage breast cancer and premalignant disease. Other screening modalities include breast self-examination by patients and clinical breast examination by physicians, which are often included with mammography in organized screening programs. This review focuses specifically on the effectiveness of mammography, attempting to isolate the data for this test alone, but much of the evidence and effectiveness of screening mammography involves combinations of tests. The review also does not address new technologies, such as digital or computer-assisted mammography or screening of women with genetic risk factors such as BRCA1 or BRCA2 mutations.

Accuracy of Screening Test

Sensitivity, Specificity, and Positive Predictive Value. The reported sensitivity of mammography, according to one review, ranges from 63% to 88%; corresponding ranges for specificity and PPV are 82% to 99% and 2% to 22%, respectively (87). Because several clinical trials combined screening mammography with clinical breast examination, the performance characteristics of mammography itself are difficult to isolate. The sensitivity, specificity, and PPV reported by trials that examined mammography alone are 68% to 88%, 95% to 98%, and 4% to 22%, respectively (87). Another review, using a modified definition

of sensitivity and specificity, reported a range of 83% to 95% and 94% to 99%, respectively (177).

As the above PPV values indicate, most abnormal screening mammograms are falsely positive. Among 2,400 American women screened over 10 years (median of four mammograms per woman), 24% had at least one false-positive mammogram; the estimated cumulative risk of false positives and biopsy was 49% and 19%, respectively, after undergoing 10 mammograms (68). Lower false-positive rates are reported by some European centers (191). There is also considerable inter- and intra-observer variation among radiologists in interpreting mammograms (127).

The sensitivity of screening mammography appears to be lower for women under age 50 than for older women, approximately 14% to 20% lower in most screening trials (87;128), possibly due to differences in breast density and/or more rapid growth of cancers. Sensitivity also appears to be lower with longer intervals between examinations. In one study, the sensitivity of the first mammogram for registry-confirmed breast cancer was 99% with 7 months of follow-up but 93% and 86% with 13 and 25 months of follow-up, respectively (128).

As with any screening test, the PPV of screening mammography depends on the prevalence (pretest probability) of breast cancer. The PPV of the first screening mammogram is between 5% and 38% (126) and is generally higher with increasing age or a positive family history. In a Canadian trial, the false-positive rate for the combination of screening mammography and clinical breast examination was 7% to 10% for women ages 40–49 years and 5% to 8% for women ages 50–59 (168;169). In an American analysis of claims data, for every 1,000 women aged 65–69 who underwent mammography, 85 had follow-up testing in the subsequent 8 months (23 had biopsies); the PPV of mammograms requiring further testing was 8% for women aged 65–69 and 14% for older women (263).

Ductal Carcinoma in Situ

It remains unclear whether ductal carcinoma in situ (DCIS), which accounts for about 12% of newly diagnosed breast cancers, represents clinically significant disease or a "false-positive" result. The incidence of DCIS and of mastectomies increases with widespread screening mammography (71). In a community case series in the United States, DCIS accounted for 41% of screen-detected cancers in women ages 40–49 (153). The clinical significance of DCIS is uncertain (251). Observational data suggest that it is a major risk factor for developing invasive carcinoma, but a large proportion of DCIS cases remain indolent (192). Among women diagnosed with DCIS, the 10-year death rate from breast cancer is 3.4% (72). Diagnostic criteria for DCIS are imprecise, producing inconsistencies in differentiating low-grade DCIS from ductal hyperplasia. Whether small, nonpalpable foci require treatment and the proper treatment modalities (mastectomy, local excision, radiation, and tamoxifen) are also debated (173). There is no direct evidence from controlled prospective studies that women benefit from the early detection and treatment of DCIS (71).

Effectiveness of Early Detection

Although the effectiveness of early detection of breast cancer has been examined in observational (e.g., case-control) studies, eight randomized controlled trials of screening mammography provide more compelling evidence and are less subject to bias from confounding variables and other methodologic factors. This review therefore focuses on the trials.

The eight trials include studies from Scotland (7), Canada (168;169), and the United States (220), and four trials from Sweden: Malmo (8), Kopparberg and Ostergotland (the Two-County Study) (236), Stockholm (90), and Gothenburg (185). The study designs varied in certain important respects: the age of women at entry ranged between 40 and 74 years, the

mammograms included one or two views, and clinical breast examination was not always part of the intervention. The subjects underwent between two and six rounds of screening, at an interval that ranged from 12 to 33 months, and follow-up in the most recent reports varied between 11 and 18 years. Compliance with the first screening examination ranged from 61% in the Edinburgh study to 100% in Canada (87).

Despite these differences, the results of the trials are relatively consistent. Each reported that screening mammography reduced the risk of death from breast cancer, with relative risk reductions ranging from 3% to 32%. All but one trial reported a relative risk reduction greater than 16%. In only two trials, the American and Kopparberg studies, did the relative risk reduction achieve statistical significance. The combined data from all trials, however, were highly significant. The pooled relative risk ratio reported in one meta-analysis (across all age groups) was 0.79 (a 21% reduction in the risk of dying from breast cancer) (129). The narrow 95% confidence interval (CI) around this estimate (0.71–0.87) denotes the limited statistical uncertainty about the magnitude of benefit.

The designs of these trials were imperfect and have been criticized (26;98). A recent analysis (98) noted that six trials had imbalances in baseline characteristics and that four trials provided inconsistent data on the number of subjects. In contrast to the positive findings in other trials, the two trials that the authors considered "adequately randomized" reported no effect on breast cancer mortality (pooled relative risk, 1.04; CI = 0.84–1.27). The authors concluded that mammography screening is unjustified, but others have criticized the assumptions used in their analysis (217).

Women Ages 40–49

Controversy persists regarding the effectiveness of screening women under age 50. Most of the benefit seen in the mammography trials occurred in women who were age 50 or older when screening began. Results for women who were age 40–49 at entry into the trials have been inconsistent. Reported relative risk reductions for this age group tend to be smaller in magnitude and less statistically significant, possibly because the trials were not designed with sufficient statistical power (sample size, length of follow-up) to detect a difference in outcome for this age group. At the frequency with which mammography was conducted in the trials, the mortality benefits that do occur for women ages 40–49 appear to be delayed. A clear separation in survival curves suggesting a mortality benefit does not become apparent in most studies until 8 to10 years of follow-up, whereas benefits are observed within 4 to 5 years of screening in older women.

Because of the modest reduction in absolute benefit observed when women ages 40–49 are screened, it has been uncertain whether the lower mortality rates observed in this age group are statistically significant or due to chance. Until recently, no trial had reported reductions in mortality that were statistically significant for women ages 40–49 at the time of screening. Early meta-analyses for this age group also failed to demonstrate statistical significance. The pooled relative risk ratios reported by Kerlikowske et al. (129) and Smart et al. (226) were 0.92 (95% CI = 0.75–1.13) and 0.84 (95% CI = 0.69–1.02), respectively. A 1993 overview of the data from the Swedish trials for women ages 40–49 reported a pooled relative risk ratio of 0.90 (95% CI = 0.65–1.24) (185).

In recent years, more extended follow-up of women in the clinical trials who were ages 40–49 at the start of screening has revealed a delayed separation in survival curves that approaches or achieves statistical significance. This trend was first reported at a 1996 conference in Falun, Sweden (234). In 1997, updates from the Gothenburg and Malmö trials revealed for the first time a statistically significant reduction in mortality for this age group. The relative risk ratios were 0.56 (95% CI = 0.32–0.98) (28) and 0.64 (95% CI = 0.45–0.89) (8), respectively. A meta-analysis incorporating the new data with other clinical trial

results concluded that the pooled relative risk ratio in women ages 40–49 was 0.82 (95% CI = 0.71–0.95) (109).

The above estimates rely on subgroup analysis of the age 40–49 cohort. The only trial designed specifically to evaluate screening in women ages 40–49 was the Canadian National Breast Screening Study. This randomized controlled trial, which assessed the effectiveness of the combination of annual mammography, physical breast examination, and teaching of breast self-examination, initially reported a relative risk ratio of 1.36 (0.84–2.21) (168), which some interpreted as evidence that screening was harmful. The ratio reported at the latest follow-up was 1.14 (0.83–1.56) (170), supporting an interpretation of no effect.

The design and conduct of the Canadian trial have been targets of criticism. Questions have been raised about the randomization method, prompted by differences in the baseline characteristics of the study arms (30;135;240). However, independent investigations have disclosed no evidence that the randomization process was flawed or subverted (16;54). Critics have also asserted that the physical examination that preceded mammography may have confounded its effects, that the mammographic technique used by some centers was outdated or of poor quality, that the trial lacked statistical power, and that it included excess cases of advanced disease (135;136). To provide further evidence, additional trials of screening in this age group are under way or being considered in the United Kingdom, other European countries, and the United States (88;175).

Whether the existing evidence is sufficient to justify routine mammographic screening for women ages 40–49 is a matter of debate. Beyond concerns about statistical significance, some question the absolute benefit of screening, given the low prevalence of breast cancer in premenopausal women. Analyses in the United States suggest that 1,500 to 2,500 women aged 40–49 would require mammographic screening for 10 to 15 years to avert one death from breast cancer (26;211). In light of the 8 to 10-year delay in observing a significant separation in survival curves for women who are aged 40–49 at the start of screening, some speculate that the benefit does not occur until after age 50 and could be retained if screening was deferred until that age. In the HIP trial, for example, all of the decrease in mortality observed among women screened at age 45–49 occurred in those who had breast cancer detected at age 50–54 (221).

For their part, proponents of screening women at age 40–49 argue that the modest benefit observed in clinical trials is due to limitations in study design. The trials were not designed to test the effectiveness of screening in this age group, recruiting instead a large proportion of older women, and the studies lacked adequate sample size and duration of follow-up to detect a difference in this subgroup. They note that the trials employed outdated methods (e.g., single views) and screened women too infrequently (e.g., every 2 years) to detect rapidly growing tumors (82). They also emphasize that the age of 50 years is an arbitrary cut point that has no biologic significance; younger women with certain risk factors face the same absolute risk of breast cancer, and may benefit as much from mammography, as do older women with fewer risk factors (91).

If women do undergo screening mammography at ages 40–49, some data suggest that an annual interval may be more effective than less frequent examinations. Breast cancer appears to have a shorter mean sojourn time in premenopausal women (174;235). A greater ratio of interval cancers to total cancers among women ages 40–49 may account for the diminished effectiveness of mammography observed in clinical trials, most of which screened every 18–24 months. Only the American and Canadian trials screened women ages 40–49 annually. The limited number of women of this age in the trials gave them inadequate power to conclude whether the difference in relative risk reduction between annual and less frequent screening is statistically significant. Indirect evidence suggests that annual screening might significantly lower mortality (81) without increasing recall rates (112).

Older Women

Data to evaluate the effectiveness of screening older women are lacking because most trials had an upper age limit of 64 years. The Swedish Two-County Trial, which included women up to age 74 at the time of screening, reported a 32% reduction in breast cancer mortality (95% CI for relative risk ratio = 0.51–0.89) for women aged 75–74 at the time of randomization (50). Modeling studies also support screening women over age 65 (159), although the incremental benefit of screening beyond age 69 (especially in women with low bone mineral density) appears to be modest (130).

Potential Harms

The potential harms of screening mammography relate primarily to false-negative and false-positive results. The latter can be especially significant because of the emotional (e.g., anxiety) and physical (e.g., biopsy) implications (152). Although the psychological impact of breast cancer screening is poorly studied (147), surveys in various countries suggest that women experience increased anxiety after a false-positive result, both at short-term and long-term follow-up, and added stress when they undergo biopsy (96;99;148;156;189). In one survey, 41% to 47% of American women with suspicious mammograms expressed anxiety and worry about breast cancer (146). In a British study, psychological effects were reported for at least 5 months by 44% to 61% of women (32). About half of women with normal mammograms said that the results reduced their fears, but concerns about breast cancer persisted for 28%.

Studies do not suggest that these results affect future screening. Among American women, having had a false-positive mammogram does not diminish, and may heighten, interest in subsequent screening (36;195). Similarly, although moderate to extreme discomfort from mammography was reported by 52% of American women, it was not associated with disinterest in future testing (66).

Between 3 and 42 biopsies are performed for every 1,000 mammographic examinations to investigate abnormal results (87). At the biopsy rate in the Canadian trial, women have a 10-20% chance of undergoing biopsy at some time during 5 years of screening with annual mammography and clinical breast examination (87). The probability of undergoing biopsy for a false-positive result depends on prevalence-related factors. The false-positive rate may be higher in younger women. In the Stockholm trial, 41% to 56% of the costs related to false-positive results occurred in women who were under age 50 when screening began (90). In an American study, women ages 40–49 having their first mammogram underwent twice as many diagnostic tests per cancer detected compared with women ages 50–59 (43.9 vs. 21.9) (126).

There is no direct evidence that ionizing radiation from mammography causes breast cancer. Given a mean breast dose of 0.l rad during mammography, modeling based on data from higher levels of radiation exposure suggests that 100,000 women screened annually from ages 50 to 75 would lose 12.9 years from radiogenic cancers but would gain 12,623 years from an assumed 20% reduction in breast cancer mortality (83). The benefit-risk ratio was narrower in a Swedish model (161). Other models have estimated that mammography would detect 114 to 815 cancers for every cancer it might induce (22;144).

Summary of the Evidence

There is good evidence from eight randomized controlled trials conducted in Europe and North America that screening mammography every 1 to 2 years can reduce the risk of dying from breast cancer by about 20%. Most of the evidence comes from women ages 50–64 at the time of screening. Recent evidence suggests that women ages 40–49 may also benefit from screening mammography, but the absolute magnitude and pace of benefit is lower,

and the best results are probably obtained with annual screening. There is limited direct evidence from which to gauge the magnitude of benefit from screening women age 65 or older. For all age groups, the absolute benefit of screening mammography is limited by the low baseline risk of acquiring the disease. In some settings, 1,500 to 2,500 women must undergo screening to prevent one death from breast cancer.

The benefits of screening mammography must be weighed against its potential harms. Although the risks of radiation exposure are negligible, screening mammograms can generate false-negative and false-positive results. According to the screening trials, 12% to 37% of breast cancers are missed by mammograms. A large proportion of women without breast cancer will receive false-positive results. Women experience some psychological morbidity from anxiety when they receive reports of an abnormal mammogram and when undergoing biopsy.

SCREENING FOR PROSTATE CANCER WITH PSA

PSA is a serine protease that is elevated in most men with prostate cancer. In the early 1990s, routine screening for PSA was introduced and widely promulgated in North America, leading to a dramatic rise in the incidence of the disease (196). Similar "epidemics" have occurred subsequently in other countries (110). Older screening tests for prostate cancer, the digital rectal examination and transrectal ultrasound, are less sensitive and specific than PSA and are not reviewed here. Screening tests currently under investigation, such as prostate-specific membrane antigen and human kallikrein-2 enzyme, are also not reviewed.

Accuracy of Screening Test

Sensitivity and Specificity. A PSA concentration greater than 4 ng/dL has a sensitivity of up to 80% to 85% in detecting prostate cancer (46;117). Analyses of archived blood samples suggests that PSA elevations (and low free PSA ratios, see below) precede the development of prostate cancer as much as a decade in advance (92;193;245;246). PSA appears to be significantly more sensitive for aggressive than for nonaggressive (small, well-differentiated) prostate cancers.

PSA has limited specificity, producing false-positive results in the presence of benign prostate disease. About 25% to 46% of men with benign prostatic hypertrophy have elevated PSA values (187;219). Biological variability and differences among PSA assays can also affect accuracy (267). PSA values fluctuate by as much as 20% to 30% for physiologic reasons (134;231). The specificity of PSA is age-related. Based on population data from one region in the United States, PSA specificity is 98%, 87%, and 81%, respectively, for men ages 50–59, 60–69, and 70–79 (117).

In asymptomatic men, the PPV of a PSA value above 4 ng/dL is 28% to 35% (33;46;48; 57); i.e., two of three elevations represent false-positive results. The reported PPV when the digital rectal examination is negative is 20% (9). It is unclear whether these data can be extrapolated to healthy men screened in clinical practice. Most of the participants in these studies were either patients seen at urology clinics or volunteers recruited from the community through advertising. Such volunteers may not be representative of men in the general population (62). In one PSA screening study, 53% of the volunteers had symptoms of prostatism (46).

Techniques for Improving Specificity

Most research on PSA screening has focused on improving specificity to reduce the probability of false-positive results and unnecessary biopsies. Approaches include:

- *PSA density*: the PSA divided by the gland volume as measured by ultrasound (20). A value greater than 0.15 ng/ml may be predictive of cancer (25).
- *PSA velocity*: the rate of change in PSA over time. An increase of at least 0.75 ng/ml within 1 year has a reported specificity of 90% in differentiating cancer from benign disease (40).
- *Age- and race-specific reference ranges*: PSA values generally increase with age and are higher in certain racial groups (125;172;188).
- *Free PSA*: the ratio of free PSA to PSA bound to alpha 1-antichymotrypsin and other moieties (45). A low free PSA ratio (e.g., < 25%) is more common with prostate cancer than with benign prostatic hypertrophy. Free PSA has garnered much interest in recent years. Some recommend its use in men with total PSA values of 2.51 to 4 ng/mL to optimize cancer detection and minimize unnecessary biopsies (44). Assays for the specific moieties to which PSA binds offer promise in further reducing false-positive rates.

No single approach has yet been proven to be more accurate than the other (108;253).

Test Frequency

There is little direct evidence regarding the optimal periodicity for performing PSA tests. A cohort study suggested that few curable cancers would be missed in men with PSA values less than 2.0 ng/ml if screening occurred every 2 years (39). A modeling study suggested that biannual screening was most cost-effective (73).

Latent Prostate Cancer

Many "true positives" detected by PSA lack clinical significance. Autopsy studies suggest that 30% of men over age 50 have histologic evidence of latent prostate cancers that are unlikely to produce symptoms or affect survival (214;266). Due to the indolent behavior of most prostate tumors, men are more likely to die of other causes (e.g., coronary artery disease, stroke) before their prostate cancers progress to clinical significance or metastasize. An analysis of elderly American decedents known to have prostate cancer reported that 61% died of other causes (182). Similar findings have been reported by others (212).

A subset of PSA-detected tumors do progress and are fatal. Certain histopathologic features provide important clues regarding the likelihood of progression; observational studies and modeling data suggest that advanced tumor grade, stage, and volume increase the probability of progression and metastasis (53;69;230). Whereas men with Gleason scores of 2 to 4 face a 4% to 7% probability of dying from prostate cancer within 15 years when treated conservatively, the chances are 60% to 87% when scores are 8 to 10 (6).

The high prevalence of these findings in PSA-detected tumors suggests that they might be more clinically important than latent cancers detected on autopsy. Pathological staging of cancers detected through PSA screening and radical prostatectomy reveals extension beyond the prostate capsule, poorly differentiated cells, large gland volumes, and metastases in 31% to 41% of patients (49;70;111;163; 227). Other retrospective studies also report a high prevalence of large tumor volumes, extracapsular extension, and positive surgical margins in cancers detected through PSA screening (213; 233).

Effectiveness of Early Detection

Direct Evidence. There is little direct evidence from controlled studies that screening for prostate cancer reduces morbidity or mortality. Few studies to date have examined the benefits of screening in terms of these clinical outcomes. One observational study of digital rectal examination found evidence of benefit (118), but others have reported no effect (89;95; 198) and all have been the target of methodologic criticisms (262).

One randomized controlled trial of screening has reported preliminary results: Canadian men offered screening were reported to have a 67% reduction in prostate cancer mortality

(141). Critics have expressed concern about the design of the study: men were not randomized to screening, but rather to receiving a letter of invitation for screening, introducing a potential imbalance in volunteer bias. Substantial crossover occurred between groups, and the authors neither performed nor included an intention-to-treat analysis. The latter, applied crudely to available data, suggests no significant reduction in mortality (204).

Other randomized controlled trials of screening are currently under way in Europe (216) and the United States (97). The results of these trials will be unavailable for at least several years, leaving only indirect evidence to currently evaluate effectiveness.

Indirect Evidence. Indirect evidence that early detection improves outcome is also limited. Men with localized tumors at diagnosis appear to live longer and have higher 5-year survival rates than those with more advanced disease. Men who undergo PSA screening are more likely to have early-stage tumors at diagnosis (stage shift) (49;164;199). Ongoing screening programs and countries in which PSA screening is prevalent report that the proportion of cancers that are clinically or pathologically advanced is steadily decreasing over time (79;140;228;229). Skeptics have not been persuaded by this evidence because of concerns about lead-time and length biases.

More attention has focused recently on evidence that prostate cancer mortality rates began steadily declining in the United States (241) and Canada (165;225) within several years of the introduction of PSA screening. The same pattern has been observed in the province of Tyrol, Austria (G Bartsch & P Boyle, personal communication, May 2000) and in a locality of the United States (201), where aggressive PSA screening programs were introduced. Epidemiologists indicate that some (105), but not all (74), of this decline may be attributable to PSA screening. A decline so suddenly after the introduction of screening would be unexpected for a cancer known for its long latency. Other potential contributors to these trends (e.g., misclassification of deaths, improved treatment) therefore cannot be excluded (85).

Efficacy of Treatment for Prostate Cancer

Screening is unlikely to benefit men if an efficacious treatment is unavailable. The principal treatment options for more localized prostate cancer include radical prostatectomy, external beam or interstitial radiation therapy, hormonal treatment, cryosurgical ablation, brachytherapy, and no treatment (expectant management or "watchful waiting"). New and investigational treatments, such as gene therapy, are not reviewed here.

In men with localized prostate cancer, the stage of disease for which screening is intended, there are no controlled trials to indicate whether any treatment improves survival over watchful waiting. Studies suggesting otherwise tend to be uncontrolled case series (14;47;95;106;107;149;222;242;268), which suffer from a host of methodologic problems. These include the lack of internal control groups (to which another treatment or no treatment was offered), the selection of subjects on clinical grounds that introduce a favorable selection bias, failure to control for confounding, and defining cure and progression based on surrogate measures (e.g., PSA) rather than hard clinical endpoints. Biochemical failure is an unreliable surrogate for survival (52;120). Aside from these problems, reported survival rates in these studies differ little from expected rates after adjustment for stage and grade of disease. Some studies do report improved survival with specific treatments (4), but the differences typically lack clinical and statistical significance because of confounding variables and wide confidence intervals.

A randomized controlled trial of the effectiveness of treatment was conducted in the United States in the 1970s (102), finding no difference in 15-year survival between radical prostatectomy and watchful waiting, but the sample size may have been too small to observe an effect. Larger randomized controlled trials comparing radical prostatectomy with

expectant management are currently under way in Scandinavia (121) and in the United States (264), but the results will be unavailable for some years.

Conservative Treatment

Skepticism about the efficacy of treatment has heightened with evidence that long-term survival for localized prostate cancer may be good even without treatment. In a widely cited study, Johansson and colleagues (121) followed a population-based cohort of 223 men with initially untreated prostate cancer. After a mean follow-up period of 12.5 years, 10% had died of prostate cancer and 56% had died of other causes (121). Although regional extension occurred in over one-third of patients and metastases in 17%, the 15-year disease-specific survival rate was 81% (122). By comparison, 10-year survival rates after radical prostatectomy in the United States are 75% to 97% for patients with well- and moderately differentiated cancers and 60% to 86% for patients with poorly differentiated disease (139).

Critics of the Swedish study worry that survival rates were high because of the large proportion of older men with small, well-differentiated tumors (257). Other studies, however, have also reported high 10-year survival rates (74% to 96%) in untreated men with palpable but clinically localized prostate cancer (2;3;258). A retrospective 16-year cohort study of American patients ages 65 to 75 who underwent conservative treatment for localized prostate cancer (either no or hormonal treatment) found that life expectancy was unchanged from that of the general population if the tumor was low grade (5). Survival was reduced by 4 to 5 or 6 to 8 years, respectively, if the tumor was moderate or high grade.

Other studies have reported more pessimistic outcomes from conservative therapy. A retrospective study in Sweden reported a disease-specific mortality rate of 50% to 100% for patients with conservatively treated localized tumors, but the denominator included only men who had died of prostate cancer (12). The same denominator problem affects other studies reporting high mortality rates with conservative treatment (29). A prospective Canadian study reported that 60% of men placed in a watchful waiting program (median age of 75 years) had clinical progression (162). A study of Danish men with prostate cancer who survived for at least 10 years reported that it was the direct cause of death in 43% of cases (31).

Researchers have attempted to model the natural history of untreated prostate cancer by pooling the results of the above studies, but the assumptions used in the models are controversial. Based on six studies, one model concluded that conservative management (delayed hormone therapy but no surgical or radiation therapy) was associated with a 10-year disease-specific survival rate of 87% for men with well-, or moderately differentiated tumors and 34% for poorly differentiated tumors (53). For patients alive after 10 years, the probability of having metastatic disease was 19%, 42%, and 74%, respectively, for well-, moderately, and poorly differentiated cancers. Critics of the analysis disagree with the study's probability estimates (41;215).

A review that pooled data from 144 articles estimated that the annual risks of metastasis and death from untreated prostate cancer were low (1.7% and 0.9%, respectively) (261). This study has been criticized for including a large proportion of patients with well-differentiated tumors and those receiving early androgen deprivation therapy (256). A different review calculated higher annual rates for metastasis and death (2.5% and 1.7%, respectively), but the analysis was limited to studies of patients with palpable, localized cancers and excluded cancers found incidentally at prostatectomy (1).

Potential Harms

Screening. False-positive (and false-negative) PSA results occur commonly with screening. Based on the reported PPV of 20% to 35% (see above), two to four men with abnormal

PSA results on routine screening will not have cancer for every man that does. These individuals must generally return for one or more repeat PSA measurements and rectal examinations and/or more invasive testing (e.g., ultrasound and fine-needle biopsy) to rule out cancer. If PSA values are suspicious, one or more biopsies may be required. As with breast cancer, psychological morbidity while the patient awaits the possibility of having cancer may be significant, but few studies have been performed.

Biopsy itself carries its own morbidity. In a large American screening program, needle biopsy was performed in 18% of patients screened by digital rectal examination and PSA (46). Discomfort from the biopsy procedure is reported by half of men. Other potential harms include local infection (0.3% to 5% of patients), sepsis (0.6% of patients), and significant bleeding (0.1% of patients) (13; 57; 63;104).

Treatment. The potential iatrogenic complications of treatment are substantial. Chief among these are impotence and incontinence, but several other adverse effects are possible. Published mortality rates for radical prostatectomy are 0.2% to 2%, with lower rates reported at specialized centers or in patients under age 65 (10;42;138;158;160;176;190;261;265;268). Surgical complications have been reduced to some extent by bilateral nerve-sparing techniques and by limiting the operation to younger and healthier men; at experienced centers, recovery of erections occurs in 68% of preoperatively potent men (with bilateral nerve-sparing surgery) and 92% of men regain continence (43).

Such outcomes in experienced hands are not always reproducible in normal community practice (237). In a series of 1,291 American men, 56% to 66% of men who were potent before radical prostatectomy complained of impotence at least 18 months later, and 8% were incontinent (232). Other surveys of American patients report high complication rates (224). An audit of procedures performed in 1986–96 at American veterans' hospitals revealed major cardiopulmonary, vascular, and colorectal injury complications in 1.7%, 0.2%, and 1.8% of men, respectively (265). Complication rates are lower in healthier and younger patients (268).

The reported incidence of acute and chronic gastrointestinal or genitourinary complications from three-dimensional conformal radiotherapy are 55% to 76% and 11% to 12%, respectively (146). Comparisons across studies to contrast the relative safety of radical prostatectomy and radiation therapy are generally unreliable because of differences in study design, patient populations, and outcome measures. Patients tend to report more bowel dysfunction with radiation therapy and more sexual dysfunction with radical prostatectomy (224). At median follow-up of 14 years, patients who undergo radiotherapy report worse bladder, bowel, and erectile function than is reported for men without prostate cancer (123).

Modeling Studies of Screening and Treatment

In the absence of direct evidence, researchers have used decision analysis to model the trade-offs between the benefits and harms of screening and treatment. The models take account of potential harms by adjusting the survival for quality of life for patient utilities. Older analyses found that screening achieves minor improvements in absolute survival (155; 244), but more recent analyses that adjust for utilities have concluded that screening produces, at best, a modest gain, measured in days to weeks, or a net loss in quality-adjusted life expectancy (38; 55;137;171). The assumptions used in these models have been challenged (167).

Other decision analyses have focused on treatment. An analysis for men aged 60 to 75 concluded that treatment increases quality-adjusted survival by less than 1 year (in most cases, by less than 0.2 quality- adjusted life years) when compared with observation (86). In men over age 70 and younger men with well- differentiated disease, treatment appeared to be more harmful than watchful waiting. Critics of the analysis questioned the probabilities

for certain components of the model and the inclusion of a relatively older population of men with low-volume and low-grade tumors (21;256). The investigators emphasize that the data were adjusted for age and tumor grade. Other studies also concluded that radical prostatectomy and radiation therapy produce a net decrease in quality of life, even after adjusting for prevalent rates for sexual and urinary dysfunction (154).

A factor that influences the balance of benefits and harms at the societal level is the cascade effect of screening on stimulating inappropriate procedures. For example, the dramatic escalation in PSA screening in the United States in the early 1990s was accompanied by a striking increase in the performance of radical prostatectomies (157;265). Many of these operations, especially the large number performed on men over age 75, may not have been indicated. A similar phenomenon is becoming apparent in other countries, such as the Netherlands (229) and Australia (11).

Summary of the Evidence

PSA screening can detect 80% to 85% of prostate cancers but has a high false-positive rate. Between 65% and 80% of men with abnormal results will not have prostate cancer. Many cancers detected by PSA have histologic features associated with progression. There is, however, little direct evidence that early detection of these tumors reduces morbidity or mortality. Observational studies show little difference in long-term survival between conservative care and aggressive treatment, but regions in which PSA screening is common have noted a striking decline in mortality rates. The theoretical but unproved potential gains from PSA screening must be weighed against its potential harms. The harms of screening include psychological and physical morbidity in evaluating abnormal results, and the harms of treatment include impotence, incontinence, and other treatment complications. Modeling studies suggest that the net effect of screening on quality-adjusted life expectancy is modest, if not negative, but are subject to methodologic criticisms.

ULTRASOUND SCREENING DURING PREGNANCY

Prenatal ultrasound helps to evaluate the structure and function of the fetus, the location and morphology of the placenta, umbilical perfusion, and amniotic fluid levels. The principal targets of screening are the more accurate determination of gestational age early in pregnancy (to avoid premature intervention for purported post term pregnancy) and the early detection of multiple gestations, fetal malformations, and intrauterine growth retardation (IUGR). Alternative modalities exist for each of these target conditions: gestational age can be estimated by menstrual history; multiple gestations can be inferred from abdominal palpation and auscultation of fetal heart sounds; congenital anomalies can be detected by serum markers (e.g., maternal serum alpha-fetoprotein, human chorionic gonadotropin), amniocentesis, and chorionic villus sampling; and IUGR can be suspected on physical examination. Some of these strategies are considerably less accurate than ultrasound.

Accuracy of Screening Test

Gestational Age. Ultrasound is the most accurate method for determining gestational age, with greater sensitivity and specificity than estimates based on the last menstrual period. Measurement of the biparietal diameter early in the second trimester correlates closely with gestational age, with 90% of patients delivering within 2 weeks of the estimated due date (37;103;248). Deliveries that are postdates on ultrasound but not by last menstrual period are more likely to have low Apgar scores (249). An Australian randomized controlled trial demonstrated that ultrasound assessment of gestational age at the first antenatal visit (before

17 weeks) reduced the need to adjust dates by 10 days or more at the time of the second trimester ultrasound (60).

Multiple Gestations

Nearly one-third of multiple gestations are missed by clinical examination (80), whereas ultrasound screening detects 98% of twins (103;194). In one study, the average gestational age at detection of multiple gestations fell from 27 to 20 weeks (103). Randomized controlled trials of ultrasound screening conducted before 20 weeks found higher rates of detection of multiple gestations (83% to 100%) than with unscreened controls (60% to 76%) (17;24;77;205;255). False-positive results do occur, however. Over 20% of first-trimester ultrasound images interpreted as multiple fetuses are either artifacts or die early in pregnancy (142).

Congenital Anomalies

Ultrasound can detect cardiac, gastrointestinal, renal, limb, and neural tube defects. Reported sensitivities range from 21% to 74% for detecting major anomalies before 22 to 24 weeks of gestation (51;75;101;150;151;223). In the largest trial of ultrasound screening (59), scans at 15 to 22 and 31 to 35 weeks detected 35% of fetuses with at least one major anomaly. The sensitivity was only 17%, however, for detecting anomalies before 24 weeks, after which abortion is more difficult, risky, and in some settings illegal. The sensitivity of selective ultrasound (for specific indications) was only 11% (5% before 24 weeks). Another trial reported a sensitivity of 40% and 27%, respectively, for the detection of major fetal anomalies in the routine screening and control groups (206).

Sensitivity tends to be higher for defects of the central nervous system and urinary tract than for the heart and great vessels (101). Sensitivity is also generally higher at tertiary care centers than elsewhere (35% vs. 13% in the largest trial [59]). Rates also differ among institutions. In one trial, for example, the sensitivity of screening before 20 weeks at two hospitals was 36% and 77% (205). Sensitivity appears to improve over time. One center reported that sensitivity rates before 23 weeks increased from 21% in 1984–89 to 41% in 1990–92 (151).

The specificity and PPV of ultrasound in detecting congenital anomalies is reportedly as high as 100% and 94%, respectively (151). The PPV was 62% in a Swedish program in which scans were performed by midwives (75). The reported false-positive rate varies across studies because of differences in study design, populations, and definitions of fetal abnormalities. Reported false-positive rates in case series are 0.2–1.0/1,000 (51;150;223). In the largest trial of screening, false-positive diagnoses were reported for 0.9/1,000 women scanned before 24 weeks (59). Another trial reported a false-positive rate of 2.7/1,000 (205). Ten of 30 cases with suspected major malformations were judged to be normal at follow-up examinations.

Neural Tube Defects. Ultrasound is highly sensitive in detecting neural tube defects. (This review does not consider the role of ultrasound in women with elevated levels of alpha-fetoprotein.) The sensitivity of ultrasound is about 100% for anencephaly, and the published sensitivity and specificity for spina bifida are 79% to 96% and 90% to 100%, respectively (59;124; 200; 202; 207; 250). A Norwegian study reported that ultrasound correctly diagnosed 89% of central nervous system anomalies detected on autopsy (116). Such data come from centers of expertise and from ultrasound examinations of high-risk women; lower rates would be expected in other settings.

Cardiac Anomalies. The sensitivity of 14-week ultrasound for detecting cardiac lesions in one study was 66%: 87% for atrioventricular septal defect, 65% for tetralogy of Fallot, 63% for transposition of the great arteries, 50% for aortic coarctation, and 44% for

isolated septal defects (133). A postmortem study found that ultrasound correctly diagnosed 73% of congenital heart defects (except for cases with secundum atrial septal defect) (115). Other studies report that the four-chamber view detects only 21% of morphologic cardiac defects (84).

Down Syndrome. Ultrasound is an imperfect screening test for Down syndrome. Artifacts can resemble increased translucency from a thickened nuchal skin fold, a feature of Down syndrome and other aneuploidies, and a standard, reproducible method for measuring nuchal translucency is lacking (114). In one study involving a variety of ultrasonographers examining high-risk women in the second trimester, the sensitivity of nuchal fold thickening in detecting Down syndrome was only 38% (100). In a multicenter Scandinavian study, ultrasound detected only 6% of Down cases (124). In other studies of high-risk women undergoing amniocentesis for chromosome analysis, the sensitivity of midtrimester ultrasound for detecting Down syndrome was 75% based on nuchal fold thickening, 31% for shortened humerus or femur length, and 69% based on an index reflecting nuchal fold thickness, major structural defect, and other abnormalities (23;58;184).

In these high-risk settings, the PPV of ultrasound for Down syndrome ranged from 7% to 25% but would probably be lower when performed on lower risk patients or by less experienced sonographers. Increased nuchal translucency appears to be a nonspecific marker for a wide range of fetal structural abnormalities (27;64). Ultrasound may play a role as part of a package of screening tests for Down syndrome that include serum markers such as pregnancy-associated plasma protein A, human chorionic gonadotropin, and urinary estriol (15;254).

Intrauterine Growth Retardation

Ultrasound is the most sensitive test for IUGR. A small abdominal circumference has a sensitivity and specificity of 80% to 96% and 80% to 90%, respectively, in detecting IUGR in the third trimester (34;94;180;260). The product of the crown–rump length and the trunk area has a sensitivity and specificity of 94% and 90%, respectively (179). Once again, outcomes in general practice may not be as good. A German study found that prenatal ultrasound in community practice detected only 32% of IUGR cases (119).

False-positive results are common because of the low prevalence of IUGR in the general population. An abnormal abdominal circumference at 34 to 36 weeks indicates IUGR in 21% to 50% of cases (34;94;259). These data are of limited generalizability because they are based on small sample sizes, the performance of ultrasound by experts, and the derivation of IUGR from a normal distribution.

A given proportion of newborns of small constitution are mislabeled as having IUGR because they fall below an arbitrary threshold. A study of 1,000 low-risk patients (61) examined the receiver-operating characteristic relationship between ultrasound indices and low birth weight. Adjusting the abdominal circumference threshold to improve sensitivity dramatically increased the false-positive rate. Using the 50th percentile of abdominal circumference as the threshold, the sensitivity, false-positive rate, and PPV of a 31-week ultrasound in detecting low birth weight (less than 10th percentile) were 84%, 41%, and 15%, respectively. Moving the threshold to the 25th percentile lowered the false-positive rate to 10% and increased the PPV to 29%, but it also lowered sensitivity to 46%.

Effectiveness of Early Detection

Although observational studies provide some evidence regarding the benefits of prenatal ultrasound, this review focuses on randomized controlled trials that examined the incremental benefit of routine compared with selective or targeted screening. These trials examined effectiveness in terms of maternal and neonatal measures of morbidity and mortality.

Women with generally accepted indications for ultrasound (e.g., possible fetal demise, ectopic pregnancy, and date-size discrepancy) were excluded. Several trials suffered from methodologic problems, such as inadequate reporting of results (67), improper randomization (179), and unmasking of data (218).

Thirteen such trials have been published with considerable variation in design. The interventions examined included a single ultrasound before 20 weeks (24;77;205;255); a single ultrasound at 18 to 24 weeks (93); serial ultrasound at 18 to 20 weeks and 31 to 35 weeks (17;67;78); one or two ultrasounds between 32 and 37 weeks after receiving an ultrasound before 24 weeks (65;179;218); and multiple scans every 3 to 4 weeks beginning at 24 to 28 weeks, with all subjects receiving a midtrimester scan (143;181). The largest trial to date, the RADIUS trial, randomized 15,151 low-risk pregnant women to routine ultrasound at 15 to 22 and 31 to 35 weeks or to usual care (which included ultrasounds for indications that developed after randomization) (78).

The evidence from these trials is reviewed below in terms of the effect of screening on perinatal mortality and neonatal/maternal morbidity, reduced need for induction of labor, and improved outcomes from early detection of congenital malformations, multiple gestations, and IUGR. It includes results from a meta-analysis by the Cochrane Collaboration (178). Due to concerns about apparent inconsistencies in results and methodology of the Aselund trial (67), the Cochrane authors reanalyzed that trial's data and included in its report only data from singleton pregnancies (except for perinatal mortality estimates) (178).

Perinatal Mortality

Among the seven trials that evaluated ultrasound before 20 weeks, four trials showed no effect on perinatal mortality (17;24;78;255), two showed a nonsignificant reduction (67;77), and one reported a statistically significant reduction in deaths (205). In the latter study, a large proportion of women whose ultrasound examinations revealed congenital anomalies elected to terminate their pregnancy. There was no difference in death rates when these induced abortions were included as deaths in the analysis.

Although a 1993 meta-analysis (35) reported that the overall reduction in death rate in the four trials available at the time (17;77;205;255) did achieve statistical significance, it found no difference in the live birth rate (reflecting induced abortions for malformations). The pooled odds ratio was 0.99 (95% CI = 0.88–1.12). This meta-analysis preceded publication of the largest study, the RADIUS trial (78). That trial, a subsequent South African trial (93), and the Cochrane meta-analysis in 1999 (178) all reported no significant difference in perinatal deaths.

Neonatal and Maternal Morbidity

Most trials have found that routine ultrasound is not associated with a statistically significant reduction in neonatal morbidity (e.g., low birth weight, low Apgar scores, neonatal seizures, admission to special care nursery, mechanical ventilation) or adverse maternal outcomes (antenatal visits or hospitalization) (17;24;77;93;205). Although one trial of early second-trimester ultrasound did report a statistically significant improvement in birth weight (from 3,479 gm to 3,521 gm) (255), another trial reported that ultrasound was associated with an increased incidence of low birth weight (93).

The RADIUS trial reported a slightly lower rate of tocolysis in screened women (3.4% vs. 4.2%), but no other differences were observed for maternal outcomes (e.g., amniocentesis, tests for fetal well-being, external version, cesarean section, or length of hospitalization) or in perinatal morbidity (78;145). Meta-analyses generally confirm a lack of benefit for most morbidity measures (e.g., low Apgar score) (35;178;243).

Benefits of Detecting Multiple Gestations

Given the excellent sensitivity of ultrasound in detecting multiple gestations, it is not surprising that clinical trials demonstrate that routine ultrasound screening reduces the rate of undiagnosed multiple gestations (178). No trial, however, has reported a significant improvement in outcomes for multiple gestations in association with ultrasound screening (except for less frequent use of tocolytics in the RADIUS trial). The number of cases of multiple gestation in screening trials may have been too small to detect such an effect.

Benefits of Detecting Congenital Malformations

One objective of screening for congenital anomalies is to give parents the opportunity to terminate pregnancies, but evidence that this occurs is inconclusive. Although one trial reported that screening before 20 weeks was associated with an increased rate of elective abortions (and thus reduced perinatal deaths) (205), the RADIUS trial observed no such effect (78). The Cochrane meta-analysis, however, concluded that ultrasound aimed at detecting congenital anomalies was associated with an increased rate of planned terminations (pooled odds ratio 3.19 [95% CI = 1.54–6.60]) (178).

Another argument for screening is that early detection of congenital anomalies might improve survival by enabling preparation for more intensive medical and surgical treatment. The RADIUS trial observed no significant improvement in survival rates among infants born with acute life-threatening anomalies (59;78). In other trials of ultrasound screening before 20 weeks, the number of anomalies detected was too small to detect a difference in outcomes.

Benefits of Detecting Intrauterine Growth Retardation

Eight randomized controlled trials have examined the health benefits of routine third-trimester ultrasound examination of fetal anthropometry (17;65;67;78;143;145;179;181;218). They reported no significant reductions in low Apgar scores, use of special care nursery, low birth weight, preterm delivery, perinatal morbidity, or perinatal mortality (excluding lethal malformations). The Cochrane meta-analysis reached similar conclusions, even for perinatal mortality without lethal malformations (178). Six trials involved low-risk patients or pregnant women selected from the general population.

A trial that examined the incremental benefit of information on placental grade from third-trimester ultrasounds (in women scanned at midtrimester and twice in the third trimester) reported a significant reduction in meconium staining at labor, low 5-minute Apgar scores, and perinatal mortality in normally formed babies (197). Another trial examined the benefit of providing Doppler ultrasound findings in cases of suspected IUGR (183). In the intervention group, clinicians were advised against hospitalizing women for suspected IUGR if the Doppler results were normal. The intervention did not appear to be effective. Although hospital stays were shorter, the hospitalization rate was unchanged. Perinatal outcome, neurologic development, and postnatal growth were similar between groups.

Effect on Induction of Labor

In four trials (67;93;145;255), dating by second-trimester ultrasound was associated with significant reductions in inductions of labor for post-term pregnancy. Although no such effect was seen in two trials (17;77) or in an early meta-analysis (35), the Cochrane meta-analysis confirmed a significant reduction in inductions for post-term pregnancy (pooled log odds ratio of 0.61 [95% CI = 0.52–0.72]) (178). It is unclear whether the overall induction rate (for all indications) is reduced. Most trials (17;24;67;77;145;255) and meta-analyses (35) have observed no such effect. In the RADIUS trial, the significant decrease in inductions for post-term pregnancy was offset by increases in inductions for

IUGR (145). Meta-analyses reveal significant heterogeneity among studies (35;243), suggesting that differences in induction rates may reflect different practice patterns associated with countries, healthcare cultures, or specific time periods.

Potential Harms

Harmful biological effects of ultrasound on the fetus have been considered but not substantiated (19). Although animal data suggest a link between fetal ultrasound and low birth weight (186;238;239), there is little supporting evidence of an effect on humans. One controlled trial reported that ultrasound screening was associated with a higher incidence of low birth weight and with nonsignificant reductions in height, body circumference, and skinfold thickness (76;181), but these were not the primary endpoints of the study.

Concerns about neurologic harm have been studied but appear unsubstantiated. Swedish children aged 8 to 9 years whose mothers participated in a trial of ultrasound screening had no greater incidence of disordered speech, motor development, behavior, hearing, or vision than did those who were not screened (131;132). Eight- to nine-year follow-up of singleton births from two Norwegian trials (in which 19% of control subjects received ultrasound) reported no difference between groups in terms of infant development, school performance, dyslexia, or parental assessment of attention levels, motor control, or perception (208). A possible association between ultrasound and nonright-handedness requires further investigation (209).

Evidence of psychological harms to parents is mixed. Although some reports suggest that prenatal ultrasound has such effects (e.g., anxiety over early and false-positive diagnoses of fetal abnormalities), other studies suggest that the examinations decrease parental anxiety about pregnancy and maternal discomfort (113;166;247;252;269). An Australian trial found that women who had a first-trimester ultrasound reported less worry and greater relaxation about their pregnancy than did control subjects (60). A Norwegian study compared women who terminated their pregnancies based on ultrasound results with those who experienced spontaneous abortion or perinatal death. There were no significant psychological differences over 1 year except for the first few days, during which the latter group experienced greater depression, intrusion, and avoidance symptoms (210).

Decision analytic models suggest that the benefits of prenatal ultrasound tend to outweigh its harms, depending on the specificity of the test and the value women assign to the reassurance of a normal result (203).

Summary of the Evidence

Prenatal ultrasound screening may reduce perinatal deaths, primarily by increasing early elective abortions for congenital anomalies, but it does not appear to lower live birth rates. Nor has it been shown to reduce neonatal or maternal morbidity. Ultrasound does enable women to know whether they have multiple gestations, congenital anomalies, or IUGR, but direct health benefits from having this knowledge have not been proved. The more accurate estimate of gestational age reduces the frequency of inductions for post-term pregnancy, but overall induction rates are not lowered, possibly because inductions for IUGR may be increased. Routine scans generate false-negative and false-positive results. Although such information can have adverse psychological effects, it can also decrease parental anxiety. Evidence from animal data that fetal ultrasound lowers birth weight and of adverse neurological effects on children have not been substantiated.

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