The Long-Term Effects of False-Positive Mammograms

TO THE EDITOR: We acknowledge Brewer and colleagues’ work in their systematic review of the long-term effects of false-positive mammography (1). We are currently conducting several projects on the psychosocial consequences of having a false-positive cancer screening result, and we would like to contribute some of the knowledge gained from our research.

In a systematic review about the adequacy of measuring short- and long-term consequences of false-positive screening mammography (2), we concluded: “Given the inadequacy of the measurement instruments used, any current conclusions about the long-term consequences of false-positive results of screening mammography must remain tentative.” In our recent research, we have found that even the most adequate measure of short-term, psychosocial consequences of false-positive screening mammography lacks validity in the setting of abnormal screening mammography (3). Therefore, we are surprised that Brewer and colleagues did not discuss the invalidity of the results on the psychosocial aspects and health-related quality-of-life aspects reported in their review.

We have conducted 6 focus group interviews with women who had been screened for breast cancer in the year before the interviews and had been told that their screening mammography was abnormal. All had also undergone additional medical procedures before the cancer suspicion was disproved. On the basis of the results from the group interviews, we developed a questionnaire specifically measuring the long-term consequences of false-positive screening mammography. The new instrument has been validated using the item response theory model: the Rasch model (until now published in a PhD dissertation [4]). We are currently using this new measure in a Danish survey, and the instrument has been translated into English, Dutch, and Norwegian. These versions will probably be used in future surveys, and they will hopefully bring new, more detailed and valid information about the possible psychosocial, long-term consequences of false-positive screening mammography.

Brewer and colleagues found national differences in breast cancer screening participation rates. In countries with national mammography programs in which government authorities invite citizens to screening, participation has been shown to induce a feeling of obligation, rather than a voluntary offer or proposal (5, 6). This might be a plausible explanation as to why breast cancer screening participation rates are higher in Europe than in the United States. Most women participating in our focus group interviews stated that having a false-positive screening mammography had frightened them so much that they did not dare to stay away from the next screening round.

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Potential Financial Conflicts of Interest: None disclosed.

References

TO THE EDITOR: We read Brewer and colleagues’ systematic review (1) with great interest. False-positive mammography happens frequently in the United States, and it is important to understand the ramifications of these test results. However, we found the opening sentence of the article misleading: “Regular mammography has become part of routine health care in the developed world for women 40 years of age or older.” Most women in the developed world do not start breast cancer screening at age 40 years. To open the article with this statement adds to the confusion about what is recommended and practiced throughout the world. According to the International Breast Cancer Screening Network’s 2002 survey, only the United States, Iceland, Sweden, and Uruguay offer screening at age 40 years (2). The 15 other member countries either start at age 45 years (2 countries) or age 50 years (13 countries) (3).

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Potential Financial Conflicts of Interest: None disclosed.

References

IN RESPONSE: Drs. Brodersen and Thorsen’s letter refers to their review showing long-term effects of false-positive mammography results in only 2 studies (1). Their findings, paired with their concerns about the validity of measures used, led them to conclude that available measures were inadequate to detect long-term effects of false-positive results. We believe that their conclusion is incorrect, resulting from their decision to exclude many ad hoc measures in order to focus on those for which some information on validation was available. In our systematic review of 23 studies that met stringent quality criteria, we found that false-positive mammograms were consistently
associated with poorer long-term outcomes on breast cancer–specific measures of well-being (for example, distress and anxiety). We chose to include breast cancer–specific measures, despite the fact that most were ad hoc, because we expected that they were more likely to detect effects of breast cancer screening than more general well-being measures with established validity. Although it is reasonable to be concerned that ad hoc measures could present problems for comparisons across studies, research supports the use of such measures to assess subclinical distress (2). In our systematic review, studies that used previously validated general distress measures that were not specific to breast cancer showed no discernable pattern of long-term effects of false-positive results. Thus, it seems that the more important issue is to make sure that the effects of false-positive results are assessed with breast cancer–specific measures of distress. We welcome the development of a better measure of breast cancer–specific distress that improves upon existing measures by establishing convergent and discriminant validity (3).

Drs. Brodersen and Thorsen seem to have misunderstood our finding of different long-term effects of false-positive mammograms on return for mammography in Europe relative to the United States. Although overall return for mammography was higher in the European studies (85%) than in the U.S. studies (60%), our paper focused on the finding that false-positive results increased return for mammography in the United States (relative risk, 1.07 [95% CI, 1.02 to 1.12]) but not in Europe (relative risk, 0.97 [CI, 0.93 to 1.01]). Although our rates of return are similar to rates previously published (4), we believe that our paper’s more important contribution is highlighting the real and lasting effects of false-positive mammograms.

We appreciate the thoughtful comments by Drs. Geller and Pinckney that more accurately characterize mammography screening guidelines for European women age 40 to 49 years.

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TO THE EDITOR: Despite their stated goal of providing women with facts so that they can make informed decisions about mammography screening, the Clinical Efficacy Assessment Subcommittee of the American College of Physicians (1) has actually done just the opposite and has provided dangerously misleading and scientifically unjustified misinformation on the subject. They are clearly uninformed about the topic of mammography screening. A clear, significant decrease in breast cancer deaths is evident in screening women beginning at age 40 years—both from randomized, controlled trials, as well as when screening is introduced into the general population.

The age of 50 years has no relevance for mammography screening. No parameter of screening changes abruptly at age 50 years or at any other age unless the data are grouped—falsely making the age of 50 appear as a real change point (2–4). Anyone claiming that age 50 years has any relevance should be required to provide ungrouped data that support this.

Those who review the randomized, controlled trials of screening should be aware that the trials were by “invitation”; therefore, they underestimate the benefit from screening (5). The committee also failed to understand that the randomized, controlled trials were not designed to permit evaluation of women age 40 to 49 years as a separate subgroup. The unplanned, retrospective subgroup analyses of women age 40 to 49 years, which have misled physicians and women for years, were using data that lacked any statistical power to permit this and should have never been used to make medical recommendations (6). Nevertheless, with longer follow-up, the analyses show a statistically significant decrease in cancer mortality rates for these women that is as high as 44% (actually higher than that for women age ≥50 years).

The committee should have realized that the National Breast Screening Study of Canada (the only trial with more deaths among the screened women than among the control participants, and whose data drop the benefit from 26% to 15%) violated the basic rules of randomized, controlled trials. Their unblinded study design would never be allowed today because it permitted compromise of the trial’s integrity, and the data clearly show this (2, 3, 7, 8).

What the committee failed to realize is that the author of the concept that screening saved lives for women in their forties because they reached the age of 50 years has recanted his conclusion, and he now agrees that most of the benefit was due to screening before 50 years of age (2, 3).

Adding additional support for screening women in their forties are the data from Sweden, where accurate data are collected. Since the introduction of mammography screening into the general population, the mortality rate has dropped by almost 50% for women in their forties, primarily due to screening. There has also been a decline in the mortality rate from breast cancer in the United States since 1990, primarily as a result of mammography screening, which includes women in their forties.

The ACP have no data to support recommending that women in their forties be screened on the basis of their individual risk for breast cancer. None of the trials stratified by risk. Furthermore, screening only women at increased risk for breast cancer will miss 75% to 80% of cancer cases.

Finally, it is not clear why the ACP would single out women in

References
their forties. All women (not just those in their forties) should be informed of the risks and benefits of any medical intervention.

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References

IN RESPONSE: Our recommendations are based on a thorough review of high-quality, scientific evidence for both the benefits and risks of screening mammography. We are recommending that all women age 40 to 49 years have an opportunity to participate in the decision whether to undergo screening, with full information about the benefits and risks from screening mammography. The individualized decision about screening mammography should be tailored to each woman and should include an assessment of her risk for breast cancer, a discussion of the benefits and risks of screening mammography, and a discussion of her concerns about breast cancer or risk associated with screening mammography. We support women getting screening mammograms as long as they are fully informed. If a woman decides to defer screening mammography, we recommend that the decision should be revisited every 1 to 2 years.

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CLINICAL OBSERVATION

Pegvisomant-Induced Lipohypertrophy: Report of a Case with Histopathology

Background: In a recent report, Maffei and colleagues (1) described 2 patients who developed subcutaneous lipohypertrophy in the abdomen during pegvisomant therapy (Somavert, Pfizer, New York).

Objective: To describe the effect of pegvisomant-induced lipohypertrophy on insulin-like growth factor I (IGF-I) levels.

Case Report: A 50-year-old woman with active acromegaly was prescribed subcutaneous pegvisomant, 10 mg/d, after a lack of response to somatostatin analogues. After 2 months of therapy, IGF-I levels decreased to within the normal range and the pegvisomant dose could be reduced (arrow).

The dashed lines span the normal range of IGF-I levels. After rotating the site of injection, IGF-I levels decreased to within the normal range and the pegvisomant dose could be reduced (arrow).
levels reached the low normal range (Figure 1). After 4 months of therapy, IGF-I returned to pretreatment levels. The IGF-I levels did not reach the normal range despite the pegvisomant dose being increased (Figure 1). At month 8, a thorough clinical examination revealed a soft, painless swelling at the left arm at the injection site (Figure 2, left). The mass was soft, rounded, movable, and skin-colored; the size was about 10 cm in diameter. Ultrasonography confirmed focal accumulation of subcutaneous adipose tissue in the patient’s left arm, with no deposition in the right arm (Figure 3). A biopsy of the mass, performed after informed consent, showed normal subcutaneous adipose tissue (Figure 4, top). At higher magnification, normal-appearing mature adipocytes, with no fat necrosis and no inflammatory cells, were found (Figure 4, bottom). Antipegvisomant antibodies were negative. The patient reported that she was using only her left arm, because she was afraid of using other sites. The patient was advised to avoid this site for future injections. One month later, the mass had nearly resolved (Figure 2, right), but a new deposit had formed on her left abdomen, the new site chosen by the patient. She performed a correct rotation technique, and 2 months later, IGF-I levels returned to the normal range with the same pegvisomant dose. At 4-month follow-up, the pegvisomant dose was gradually reduced from 30 mg/d to 20 mg/d, with normal IGF-I levels 4 months later (Figure 1).

Discussion: Pegvisomant is a biosynthetic analogue of human growth hormone that functions as a growth hormone receptor antagonist (2). It is generally well tolerated, but adverse effects (including local reactions), such as a mild rash, have been reported (2, 3). Lipohypertrophy is characterized by a benign enlargement of fat tissue secondary to adipose subcutaneous deposition. It has been associated with some hormonal injections (4). The pathogenesis of lipohypertrophy secondary to pegvisomant therapy is unclear. It could be linked to the local lipogenic action of pegvisomant, because both growth hormone and IGF-I have physiologic roles in adipose metabolism. They enhance lipolytic activity, which results in a reduction of accumulation.
Little is known about the natural history of pegvisomant-induced lipohypertrophy, because follow-up has not been reported (1). In our case, lipohypertrophy resolved less than 1 month after stopping the injections. Also, better IGF-I control was achieved by rotating the injection site, suggesting decreased pegvisomant absorption from the lipohypertrophic site.

Conclusions: Lipohypertrophy secondary to pegvisomant is not limited to the abdomen and may be rapidly reversible after treatment withdrawal. Patients should be instructed to routinely rotate the injection site, and physicians should specifically look for lipohypertrophic lesions in patients who do not respond to pegvisomant therapy.

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References

Correction: “Doctor, How CERTain Are We That This Diabetes Medication Is Best for Me?”

In a recent editorial (1) discussing Bolen and colleagues’ systematic review (2) on the effectiveness and safety of oral medications for type 2 diabetes mellitus, an important error was discovered after printing. Bolen and colleagues’ review was commissioned by Agency for Healthcare Research and Quality under the Effective Health Care Program and its Evidence-based Practice Centers, not the Centers for Education and Research on Therapeutics program, as originally stated. Corrections have been made throughout the online version of the editorial to rectify this error.

References
1. Pogach LM. “Doctor, how CERTain are we that this diabetes medication is best for me?” [Editorial]. Ann Intern Med. 2007;147:428-30. [PMID: 17652707]