CORRESPONDENCE

Re: Tumor Characteristics and Clinical Outcome of Elderly Women With Breast Cancer

The conclusion reached by Diab et al. (1) that “screening mammography might have limited value in older patients” is flawed because of the misinterpretation of two observations. First, Diab et al. observed a pattern of increasing survival with advancing age among women with early-stage breast cancer and inferred that older women have more indolent disease. In fact, this pattern likely is due to the selection of healthier women for screening and surgical staging. Second, they misinterpreted the importance of the observation that breast cancer accounts for a decreasing proportion of total mortality as women age.

Screening bias best explains the authors’ observation that relative survival increases with age among women with small tumors (<2 cm). Women older than 65 years who obtain screening mammograms are healthier than their peers who are not screened (2). Relative survival improves with age because older women with screen-detected tumors are less likely to have serious, comorbid disease than their age-matched peers in the general population. This pattern is not due to a more indolent type of breast cancer in older women. When we specifically examined cause-specific mortality in the Surveillance, Epidemiology, and End Results (SEER) population, we found no decrease in breast cancer mortality with advancing age (Table 1) (3).

Staging bias accounts for the authors’ observation that the relative survival of women with pathologically negative lymph nodes increases with age (1). Women older than age 70 years who undergo lymphadenectomy for pathologic lymph node evaluation have less comorbid disease than those who do not (4). The proportion of women who are pathologically staged in the SEER population decreases with advancing age (Table 1). When we reanalyzed the data and included women clinically staged, the age difference in relative survival was much reduced. Moreover, when we examined breast cancer mortality for women with lymph node-negative disease, we found no decrease in breast cancer mortality with advancing age (Table 1). Thus, the clinical outcome for women with lymph node-negative disease or tumors less than 2 cm does not improve with advancing age.

Diab et al. (1) correctly observed that the proportion of total mortality due to breast cancer decreases with advancing age. This is true only because other causes of death become more common. The critical observation for screening policy is that breast cancer incidence and mortality rates both increase with advancing age (5). The appropriate application of the observation by Diab et al. lies instead at the level of the individual patient, where competing mortality risks should play a role in predicting mammography benefits for each individual regardless of age.

Does screening mammography reduce breast cancer mortality among women older than age 70 years? Observational data (6) suggest that mammography already has contributed to decreased breast cancer mortality rates for women aged 70–79 years. In addition, screening mammography detects early-stage disease as effectively among women aged 70 years and older as among women aged 50–69 years (7). Correctly interpreted, observational data suggest that screening mammography decreases breast cancer mortality among women aged 70 years and older as it does among women aged 50–69 years.

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TIM BYERS

Table 1. 8-year breast cancer mortality and relative survival for tumors less than 1 cm, for tumors 1–1.9 cm, and for lymph node-negative disease by type of staging*

<table>
<thead>
<tr>
<th>Age, y</th>
<th>50–54</th>
<th>55–59</th>
<th>60–64</th>
<th>65–69</th>
<th>70–74</th>
<th>75–79</th>
<th>80–84</th>
<th>≥85</th>
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</thead>
<tbody>
<tr>
<td>8-y breast cancer mortality; †%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor &lt;1 cm</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>14</td>
<td></td>
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<tr>
<td>Tumor 1–1.9 cm</td>
<td>8</td>
<td>10</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Pathologically staged lymph node-negative disease</td>
<td>7</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>11</td>
<td></td>
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<tr>
<td>Clinically or pathologically staged lymph node-negative disease</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>13</td>
<td></td>
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<tr>
<td>8-y relative survival; ‡%</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Tumor &lt;1 cm</td>
<td>96</td>
<td>95</td>
<td>99</td>
<td>101</td>
<td>100</td>
<td>99</td>
<td>109</td>
<td>90</td>
</tr>
<tr>
<td>Tumor 1–1.9 cm</td>
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<td>93</td>
<td>92</td>
<td>97</td>
<td>99</td>
<td>107</td>
<td>102</td>
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<tr>
<td>Pathologically staged lymph node-negative disease</td>
<td>94</td>
<td>92</td>
<td>96</td>
<td>97</td>
<td>99</td>
<td>101</td>
<td>107</td>
<td>115</td>
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<tr>
<td>Clinically or pathologically staged lymph node-negative disease</td>
<td>93</td>
<td>92</td>
<td>95</td>
<td>96</td>
<td>98</td>
<td>97</td>
<td>100</td>
<td>91</td>
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<tr>
<td>Proportion of total invasive cases with pathologically staged lymph nodes, %</td>
<td>89</td>
<td>88</td>
<td>86</td>
<td>87</td>
<td>85</td>
<td>80</td>
<td>70</td>
<td>48</td>
</tr>
</tbody>
</table>

*Data from Surveillance, Epidemiology, and End Results (SEER) nine-registries population: invasive breast cancer cases diagnosed 1988–1989 (3).
†Proportion of women diagnosed with invasive breast cancer in 1988–1989 for whom breast cancer was the underlying cause of death within 8 years of diagnosis.
‡Relative survival is the ratio of observed survival among women with breast cancer to the expected survival for the age-matched, general population of women.

REFERENCES

(3) Surveillance, Epidemiology, and End Results (SEER) Program Public-Use CD-ROM (1973–1996), National Cancer Institute, DCCPS.

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of women in general. But I believe it is premature to suggest that “This favorable outcome should be considered when making clinical decisions in older patients” (1), since the relative survival among women with lymph node-negative disease is close to 1.0 irrespective of age. According to the authors’ data, the relative survival is 0.95 (95% confidence interval [CI] = 0.93–0.97) for women 50–54 years old versus 1.09 (95% CI = 0.98–1.20) for those 80–84 years of age. This is a modest difference that, whether statistically significant or not, is of no clear clinical significance. These observations do not in any case support the authors’ contention (1) that “it is possible that screening mammography might have limited value in older patients.” If it were truly the case that older women fare particularly well when their breast cancer is identified while still lymph node negative, that would argue in support of particularly aggressive screening in this group of women.

On the basis of their perception of differences in prognosis in relation to age of postmenopausal women with breast cancer, Diab et al. (1) also contend, “The best approaches to local and systemic treatment in elderly patients . . . require evaluation in clinical trials” conducted among such patients, since treatment recommendations based on randomized controlled trials of breast cancer conducted in younger postmenopausal women “…might not apply to older patients.” However, since I do not share their perception, I believe that if a treatment has been convincingly demonstrated to be efficacious in trials restricted to postmenopausal women who are not elderly, it would now be unethical to conduct a new trial of elderly women in which that treatment would be withheld from some participants.

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RESPONSE

The following are our responses to the issues raised by Drs. Basche and Byers and by Dr. Weiss.

In response to Basche and Byers, the observation that the relative survival of elderly patients with early breast cancer improves with advancing age is probably related to more than one factor. The association between increasing age and more favorable biologic characteristics, as clearly shown in Table 1 in our article (1), is one factor. We agree with Basche and Byers, as we indicated in our discussion (1), that “...the distribution and impact of other comorbid conditions on survival might be different in the breast cancer population and the population at large.” Patients who receive screening mammography tend to have better access to medical care and are healthier. Although screening bias cannot be excluded as a factor, the same trends in relative mortality were seen in the San Antonio database, a cohort mostly from the 1970s and mid-1980s, a period during which screening was not widespread or even common. The result, regardless of the cause, is that women with early breast cancer tend to have survival similar to that of the population at large. Whether the survival of elderly patients with mammography-detected tumors is superior to that of screened patients without breast tumors can only be answered by prospective trials that take comorbidity into consideration.

The analysis performed by Basche and Byers showing that breast cancer mortality is the same across all age groups does not conflict with any of our analyses or conclusions. We clearly showed in Table 4 of our article (1) that the relative contribution of breast cancer death to the overall causes of mortality decreases with advancing age, and this observation mainly related the increasing contribution of comorbid conditions to overall mortality. The result, again, is that breast cancer is not the main cause of death in elderly breast cancer patients, and this result has clinical implications for population-based screening strategies. In addition, one should take into consideration that older patients are less likely to receive local and systemic therapy (as shown in our article and by others) than are younger patients, which could explain the similar breast cancer mortality across age groups, in spite of
having more indolent disease. The interaction between therapy and breast cancer mortality in elderly patients needs to be evaluated in prospective clinical trials to delineate the impact of tumor biology, therapy, and comorbidity on survival. We agree, however, that individual health management decisions should be tailored to a specific patient or person.

We believe that the impact of screening mammography on mortality in women older than 70 years should be evaluated in prospective clinical trials rather than by extrapolation or indirect observation.

In response to Weiss, our conclusion should have stated “breast cancer survival in older women with early breast cancer is similar to survival in the general population irrespective of disease status.” “Irrespective of disease status” refers to the general population where few women do have breast cancer. We regret inadvertently omitting early breast cancer, and we take this opportunity to clarify our conclusion.

Our statement (1), “This favorable outcome should be considered when making clinical decisions,” is based not only on the relative survival of elderly patients but also on the decreasing contribution of breast cancer to overall mortality in older patients. This should be considered when making clinical decisions in elderly patients in general and especially in patients with comorbid conditions. This applies to screening older patients for breast cancer. Because of the increased contribution of non-breast-cancer deaths to the overall mortality, it is possible (but unknown at this time) that mammography screening in an elderly population may not be as effective because of a change in biology and competing causes of mortality.

There is a paucity of direct data examining breast tumor biology, treatment effects, and the interaction of therapy with comorbid conditions in elderly breast cancer patients. Rather than use of extrapolation to guide management, inclusion of elderly patients in randomized trials directly examining these issues would be wise. Given the incidence of the problem, such trials should not, in principle, be difficult to complete.

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NOTES

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