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## Reply to Flawed Assumptions Used to Defend Screening Mammography

We are pleased to have the opportunity to respond to Bleyer et al. As our recent article<sup>1</sup> in *Cancer* shows and their comments confirm, the assessment of changes in

breast cancer stages over long time periods and the implications for the overdiagnosis of invasive cancer hinge sensitively on assumptions about the trend in background breast cancer incidence rates. We provided various measures of background incidence trends in the absence of screening mammography, cited other estimates from the literature, and modeled a range of annual percentage change (APC) values from 0.5% to 2.0%. Our article shows that a reasonable background incidence increase, independent of screening mammography, leads to a reduction in late-stage disease. It is, therefore, not surprising that the authors of the letter argue that our assumption of a background incidence APC increase in US women from 1977–1979 to 2007–2009 is too high. Bleyer and Welch’s estimate of overdiagnosis assumed an increase of 0.25% per year on the basis of background trends for women less than 40 years old.<sup>2</sup>

In fact, our assumption of a 0.5% to 2.0% APC is quite modest. Our article cites numerous published examples of APCs in excess of our central estimate of 1.3% among unscreened women.<sup>1</sup> Additional recent publications support the reasonableness of our central estimate:

1. National Cancer Institute–funded Cancer Intervention and Surveillance Modeling Network (CISNET) models estimated background breast cancer mortality trends absent screening mammography and adjuvant therapy from 1975 to 2000.<sup>3</sup> The median of 7 different CISNET models estimated a 31% expected increase in the mortality rate secondary to background incidence trends or an average increase of 1.2% per year.
2. In Iceland, where population-based screening began in late 1987, over the prescreening period of 1969–1987, the breast cancer incidence for women who were 40 to 69 years increased 1.4% per year.<sup>4</sup> Twenty-three years after screening began, the invasive cancer incidence was 11% lower than expected on the basis of prescreening incidence trends. This reduction in the incidence of invasive cancer after screening is nearly identical to our 9% reduction estimate at an APC of 1.3%.
3. In Denmark, where a national screening program did not begin until 2008–2010, among women who were 50 to 69 years and were not offered screening from 1990 to 2007, the breast cancer incidence increased 3% per year, which is more than double our estimate.<sup>5</sup> In addition, an overdiagnosis rate of 4% was reported.<sup>5</sup>
4. World data from the International Agency for Research on Cancer of the World Health Organization between

2008 and 2012 showed a 20% (or 4% per year) increase in the incidence of breast cancer and a 14% (or 2.8% per year) mortality rate increase.<sup>6</sup> The agency noted specifically that the “marked increase in breast cancers must be addressed” and attributed the increased mortality in part to an increased incidence.

Directly germane to the APC estimates in reference to late-stage disease incidence is a recent study, coauthored by Bleyer, which demonstrated an APC of 2.1% for the most lethal type of late-stage breast cancer, that with distant involvement at presentation, among women 25 to 39 years old.<sup>7</sup> If this background cancer incidence APC estimate had been used in our study, the projected decrease in distant disease would have exceeded 40%.

The authors of the letter lead the reader to believe that by 1982, clinical screening mammography in the United States was well underway and, therefore, was a major contributor to the increasing incidence trend. That was not the case. An analysis of long-term secular incidence trends in Connecticut from 1940 showed an upward inflection point of the existing trend, which was attributed to the onset of screening mammography, after 1982, not before.<sup>8</sup> Breast cancer incidence rates increased by an average of 1.3% per year from 1941-1945 to 1966-1970, many years before clinical mammographic screening in the United States.<sup>9</sup>

The referenced “national breast cancer detection demonstration program” was an experimental program that ran from 1973 to 1980 and screened 283,222 women who were 35 to 74 years (0.6% of women who were 35-74 years old). After the Breast Cancer Detection Demonstration Project ended in 1980, there was no national screening program and very little screening. Medicare did not begin funding screening mammography until 1991. From 1977 to 1982, much mammography in the United States was diagnostic mammography. Sites offering mammography often did not distinguish between screening and diagnostic mammography. Bleyer et al cite Howard<sup>10</sup> stating that “by the end of the [1977-1982] interval at least 5-10% of women in the U.S. were screened.” Howard did not state this, instead stating “it is difficult to determine the extent to which mammographic examinations have been performed for screening rather than diagnostic purposes. There is, therefore, an element of uncertainty in estimating the proportion of women who have been screened with mammography at some time in their lives and the proportion that are routinely screened.”<sup>10</sup> Other data, when screening mammography and

diagnostic mammography were tracked separately during those years, confirm that “less than 5% of women aged 45 years and older underwent the [screening] procedure each year.”<sup>11</sup>

The authors of the letter suggest that the most reliable data for establishing a nonscreened background incidence trend among older women are data for women less than 40 years old. We have provided published sources that suggest otherwise. Feuer and Wun<sup>8</sup> showed that before 1982, APCs in the United States differed by age. Women who were 40 to 49 years old had an APC of 0.8%, and women who were 60 to 69 years old had an APC nearly double that of 1.51%. Similarly, data from the United Kingdom before the onset of screening, shown in Table 1 of our article,<sup>1</sup> show that women less than 40 years old had an APC of 1.1% (similar to what we assumed for US women who were 40+ years old), whereas UK women who were 50+ years old had an APC approximately twice that (2.1% for women who were 50-64 years old, 1.8% for women who were 65-69 years old, and 2.3% for women who were 70+ years old).

Attributions of overdiagnosis or underdiagnosis of invasive cancer to mammographic screening rely on knowledge of the actual screening status of women with breast cancer. Because Surveillance, Epidemiology, and End Results (SEER) data do not track the screening status, estimates of overdiagnosis based exclusively on SEER data are limited.

The last statement of the letter is incorrect. Mark A. Helvie, Joanne T. Chang, and Mousumi Banerjee are not paid consultants of GE Healthcare.

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