

## CORRESPONDENCE

### Breast Cancer Screening for Women Aged 40–49 Years: Screening May Not Be the Benign Process Usually Thought

As reported by eight randomized trials of breast cancer screening conducted over the past 40 years, women aged 50–59 years who are screened for breast cancer have a 20%–30% survival advantage compared with unscreened control subjects. However, when women aged 40–49 years are screened, there is either no advantage or a small disadvantage to the screened population for the first 6–8 years of the trials. After that, an advantage to screening begins to appear. These data have not been explained. Data from all screening trials were presented at a National Institutes of Health Consensus Development Conference in 1997. After review, an expert panel reported that the data did not support an overall recommendation for screening all women aged 40–49 years. The consensus report was then rebuffed by the Director of the National Cancer Institute (Bethesda, MD) as well as by the U.S. Senate, as colorfully documented by Fletcher (1).

We have recently published two articles (2,3) that may explain these puzzling trial results. Briefly, analysis of clinical data suggests that the surgical removal of a primary breast tumor from premenopausal lymph node-positive women triggers the growth of temporarily dormant distant disease in approximately 20% of cases. This growth could explain an additional 0.11 deaths per 1000 screened women aged 40–49 years that occurs 2–3 years after the start of screening—approximately what is observed. We proposed that the biologic mechanism of the surgical influence on the metastatic development might be a surge of angiogenesis resulting from the removal of inhibitor(s) or even the appearance of growth factors (2). If our explanation is correct, at least five and perhaps as many as seven of the eight screening trials may no longer be relevant to current practice because they were conducted before adjuvant chemo-

therapy was routinely used for premenopausal lymph node-positive patients; such adjuvant therapy would likely attenuate the induced growth.

This same argument does not apply to the Canadian screening trial (4), which includes adjuvant chemotherapy for all lymph node-positive premenopausal patients and has found no survival advantage in the screened group, even after 10 years of follow-up. Two striking features of the Canadian trial may account for these findings. First, there was an excess of deaths in the intervention arm, which was attributed to an excess of patients diagnosed with more than three positive lymph nodes in the first year. Second, in year 1, threefold more biopsies were done in the intervention arm than in the control arm. The role that surgery plays in explaining these findings might remain unchanged. Because the breast is rich in lymphatics, the wounding associated with a biopsy might increase the secretion of growth factors and induce lymphangiogenesis (Kaipainen A: personal communication). The lack of screening benefit in the Canadian study can be explained if as few as 14 (or 2.5%) of the extra 550 biopsies done in the first year in the intervention arm showed false-negative results and caused lymphangiogenesis and stage progression. This effect is small enough that it would escape detection in anything other than a large screening trial (3). Thus, while screening *per se* is not necessarily detrimental, the resulting interventions can produce a worsened situation for a significant fraction of young women. Screening may not, therefore, be the benign process commonly thought.

The priority is to test the new theories proposed in our two articles. If they prove to be correct, various approaches can be taken to provide the full benefit of screening to women aged 40–49 years. The number of biopsies should be minimized, and the accuracy of biopsies should be kept high. Premenopausal women can be given an antiangiogenic drug during the critical few days after surgery to combat the surge in angiogenesis. Also, the careful timing of surgery may minimize the stimulation of angiogenesis, as was indicated by another study (5) that stressed the importance of menstrual cycle timing of resection. Indeed, since the serum concentration of the angiogenesis stimulator vascular en-

dothelial growth factor (VEGF) varies inversely with that of progesterone during the menstrual cycle, it could be assumed that surgery should be scheduled during those phases of a woman's cycle when progesterone concentration is elevated (6).

MICHAEL RETSKY  
ROMANO DEMICHELI  
WILLIAM HRUSHESKY

### REFERENCES

- (1) Fletcher SW. Whither scientific deliberation in health policy recommendations? Alice in the Wonderland of breast-cancer screening. *N Engl J Med* 1997;336:1180–3.
- (2) Retsky M, Demicheli R, Hrushesky W. Premenopausal status accelerates relapse in node positive breast cancer: hypothesis links angiogenesis, screening controversy. *Breast Cancer Res Treat* 2001;65:217–24.
- (3) Retsky M, Demicheli R, Hrushesky W. Wounding from biopsy and breast-cancer progression [letter]. *Lancet* 2001; 357:1048.
- (4) Miller AB, Baines CJ, To T, Wall C. Canadian National Breast Screening Study: 1. Breast cancer detection and death rates among women aged 40 to 49 years. *CMAJ* 1992;147:1459–76.
- (5) Hrushesky WJ, Bluming AZ, Gruber SA, Sothorn RB. Menstrual influence on surgical cure of breast cancer. *Lancet* 1989;338:949–52.
- (6) Heer K, Kumar H, Speirs V, Greenman J, Drew PJ, Fox JN, et al. Vascular endothelial growth factor in premenopausal women—indicator of the best time for breast cancer surgery? *Br J Cancer* 1998;78:1203–7.

### NOTES

*Affiliations of authors:* M. Retsky, Department of Surgery, Children's Hospital and Harvard Medical School, Boston, MA; R. Demicheli, Milan National Cancer Institute, Italy; W. Hrushesky, Dorn Veterans Affairs Medical Center, Columbia, SC.

*Correspondence to:* Michael Retsky, Ph.D., Children's Hospital and Harvard Medical School, Enders Bldg., 10<sup>th</sup> Floor, 300 Longwood Ave., Boston, MA 02115 (e-mail: retsky@jimmy.harvard.edu).