Curr Oncol, Vol. 19, pp. 59-60; doi: http://dx.doi.org/10.3747/co.19.1037

GUEST EDITORIAL

Disappearing breast cancers

A Countercurrents Series[a] *with S.A. Narod MD*

Epidemiologic observations in two fields of study lead to the same conclusion: namely, that a proportion of breast cancers will go away without medical or surgical intervention.

The first relevant observation is that, after cessation of hormone replacement therapy, the excess risk of breast cancer attributable to exogenous hormones dissipates within 2 years [1,2]. In countries in which the use of hormone therapy dropped rapidly after publication of the results from the Women's Health Initiative, a decline in breast cancer incidence was noticed immediately [3]. If hormone therapy increases risk by initiating new tumours, a gradual fall-off in risk would be expected because of the long latent period. The data better fit a model in which the removal of estrogen and progesterone leads to the disappearance of an already established cancer [2].

The second observation is that overdiagnosis is observed in breast cancer screening trials. That is, some cancers detectable only by mammography would never become clinically apparent (or life-threatening) [4,5]. The most compelling evidence for this observation comes from Zahl and colleagues [5] in work recently published in *Lancet Oncology*. In their observational study, one group of Swedish women was screened in year 1 and then annually for 4 years. The comparison group was screened only once, between year 4 and year 6. After the first round of screening, an excess of 324 cancers per 100,000 person–years was seen in the screened group. That is the hoped-for result in a study of a successful screening program. The excess cases could be attributed to early diagnosis (cancers that would present eventually), but also to overdiagnosis (cancers that would regress). If the entire excess is the result of the precocious detection of cancers that would eventually become symptomatic, the difference would be expected to vanish after the controls were screened. However, after the controls were screened (between years 4 and 6), the difference at 6 years—174 per 100,000 per year—persisted. Those cancers are attributable to overdiagnosis. Therefore, for every 100 nonpalpable cancers found through mammography alone, 54 would presumably have gone away (174 / 324 × 100 = 54%).

The foregoing studies highlight the dynamic nature of breast cancer [2]. Of course it is impossible to say which particular cancer will disappear without treatment, and so all must be treated. The situation is analogous to that of treating all small high-grade breast cancers with adjuvant chemotherapy—which is probably helpful only in about one third of cases—because we don't know which patient has latent metastases. But we can make some assumptions and see where they lead.

Overdiagnosis is discussed in the context of mammography; it is not identified as a problem with clinically-detected (that is, palpable) cancers or with node-positive cancers. The assumption, therefore, is that a proportion of nonpalpable mammography-detected cancers might disappear. But how many and which ones?

Presumably, factors that predict disappearance also predict a favorable prognosis. Small triple-negative cancers, cancers positive for the human epidermal growth factor 2 (HER2), and breast cancers that occur in *BRCA1* and *BRCA2* carriers often behave aggressively [6] and are unlikely candidates for overdiagnosis. It is therefore best to explore small node-negative HER2-negative cancers. Among mammography-detected nonpalpable node-negative cancers, size remains a strong predictor of prognosis. It can therefore be assumed that, the larger the cancer, the more likely it will be to progress. In the Swedish study, about one half of the mammography-detected

[a] This guest editorial is part of a series, titled Countercurrents, by Dr. Steven A. Narod. Series Editor: William D. Foulkes MB BS PhD, McGill University, Montreal, QC.

cancers progressed in the 6-year follow-up period, and about one half regressed.

The number of cancer cells is a function of tumour volume in cubic centimetres. Each cell is about 20 μm in diameter. A 1-cm cancer has about 100 million cells, a 0.5-cm cancer has about 10 million cells, and a 1-mm cancer has about 100 thousand cells. Assuming that, for small cancers, the probability of progression is proportional to the number of cancer cells, and assuming that a small screen-detected nonpalpable cancer of 1.0 cm in size has a 50% chance of progressing, then a cancer of 0.8 cm would have about a 25% chance of progressing. But a 0.5-cm cancer would have only a 6% chance of progressing, and a 1.0-mm cancer would have a 0.05% chance (1 in 2000) of progressing. Given that about 9% of women in Canada are in fact diagnosed with clinically-detectable breast cancer at some point in life [7] and that each tumour started out as a very small cancer, then the proportion of Canadian women with a 1-mm subclinical breast cancer must be extremely high. (It is accepted among pathologists and oncologists that a 1-mm lesion can in fact be a breast cancer, and so I here consider 1 mm to be the cut-off between a real cancer and something else.) It then follows that, at any time, most prevalent breast cancers must be very tiny, and almost all of them will disappear without treatment.

I am reminded of Stephen Jay Gould's essay "The Power of the Modal Bacter," wherein he argues that, by weight, most of the earth's biomass is composed of bacteria [8]. Can we get to the bottom of this issue of subclinical tumours? And can we hope to discriminate between mammographic cancers that will and will not progress?

Esserman and colleagues have preliminary evidence to suggest that the 70-gene signature might be helpful in this regard [9]. If this area is considered worthwhile for study, then I think it will be useful to collect data and specimens from mammographically-detected, nonpalpable, node-negative breast cancers. Presumably, the smaller the cancers, the more enriched they will be for factors that correlate with a propensity to disappear.

However, I also recognize that this issue is a divisive one; the premise that some cancers may disappear is not universally accepted. The argument, as outlined here, is theoretical. I both extrapolate from a small number of studies that address the topic indirectly and make several assumptions. The issue of overdiagnosis polarizes members of the scientific and lay communities because it calls into question the value of early detection and the mission to seek out breast cancers of the smallest size possible.

CONFLICT OF INTEREST DISCLOSURES

The author has no financial conflicts of interest to declare.

REFERENCES

1. Chlebowski RT, Kuller LH, Prentice RL, *et al.* on behalf of the WHI investigators. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573–87.
2. Narod SA. Hormone replacement therapy and the risk of breast cancer. *Nat Rev Clin Oncol* 2011;8:669–76.
3. Ravdin PM, Cronin KA, Howlader N, *et al.* The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007;356:1670–4.
4. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst* 2010;102:605–13.
5. Zahl PH, Gøtzsche PC, Mæhlen J. Natural history of breast cancers detected in the Swedish mammography screening programme: a cohort study. *Lancet Oncol* 2011;12:1118–24.
6. Foulkes WD, Reis–Filho JS, Narod SA. Tumor size and survival in breast cancer—a reappraisal. *Nat Rev Clin Oncol* 2010;7:348–53.
7. World Health Organization, International Agency for Research on Cancer (IARC). The Globocan Project [Web resource]. Lyon, France: IARC; 2008. [Available online at: http://globocan.iarc.fr; cited February 5, 2012]
8. Gould SJ. The power of the modal bacter, or why the tail can't wag the dog. In: *Full House: The Spread of Excellence from Plato to Darwin.* New York, NY: Harmony Books; 1996: 167–216.
9. Esserman LJ, Shieh Y, Rutgers EJ, *et al.* Impact of mammographic screening on the detection of good and poor prognosis breast cancers. *Breast Cancer Res Treat* 2011;130:725–34.

Correspondence to: Steven A. Narod, Women's College Research Institute, Women's College Hospital and the Dalla Lana School of Public Health, University of Toronto, 790 Bay Street, Toronto, Ontario M5G 1N8.
E-mail: steven.narod@wchospital.ca