Cancer Epidemiology, Biomarkers & Prevention

Editorial

Editorial on Buist et al., p. 720

An Ounce of Breast Cancer Prevention—Let's Try for a Pound

Ellen Warner

There are far too many breast cancer survivors.

Nobody would deny that the progressive drop in breast cancer mortality over the last 20 years in the developed world is a major triumph. However, over the same time period, there has been minimal change in breast cancer incidence, resulting in an ever-increasing "survivor" population (1). Many of these women will face a lifetime of physical and psychologic morbidity. In fact, at the current rate of progress in screening technology and disease treatment, we may soon be able to detect almost every breast cancer at a curable stage. But such a situation would be far from ideal at current incidence rates. Simply put, "the human and financial savings of not becoming a cancer survivor. . . makes prevention a (much) better option. . .." (2).

A welcome change to the gradual increase in breast cancer incidence in the 1990's, was the dramatic decline after 2002 (1). Determining the cause of that decline was the objective of the study by Buist and colleagues published in this issue (3). The occurrence of the drop in incidence shortly after publication of the results of the Women's Health Initiative (WHI) study showing that estrogen–progesterone hormone replacement therapy (EPT) increases breast cancer risk by at least 25% after 5 years of use (4), suggested that immediate discontinuation of EPT by a large percentage of users was the direct cause of the change in incidence. This hypothesis was further supported by the fact that the change was only seen in women older than age 50 and primarily in hormone receptor–positive tumors. However, an alternative hypothesis was that the cause was a reduction in the use of screening mammography by women who discontinued hormone therapy (HT) and might consequently be less concerned about their breast cancer risk or less likely to regularly see their physician. Less mammography could immediately decrease reported breast cancer incidence both by delaying diagnosis of many clinically significant cancers and by preventing overdiagnosis of some clinically insignificant cancers. Although distinguishing between these 2 hypotheses should have been relatively easy, there were conflicting reports about trends in mammography use after 2002 (5, 6).

Author's Affiliation: Sunnybrook Odette Cancer Centre, University of Toronto, Toronto, Ontario, Canada

Corresponding Author: Ellen Warner, Sunnybrook Odette Cancer Centre, 2075 Bayview Avenue, RmT2 053, Toronto, ON M4N 3M5, Canada. Phone: 4164804617; Fax: 4164806002;
E-mail: Ellen.Warner@sunnybrook.ca

doi: 10.1158/1055-9965.EPI-12-0312

The study by Buist and colleagues was designed to clarify this uncertainty. In a "dynamic cohort study", the investigators traced individual woman-level data on HT dispensing, mammography compliance, and breast cancer incidence, of 163,500 women aged 50 to 79 in a Group Health Cooperative. Participants were classified as EPT users, estrogen therapy (ET), users, former EPT or ET users (within 4 years of use), or nonusers, and reclassified as their user status changed. The proportion of women using any HT decreased from 41% in 1998 to 11% in 2009, with most of the decrease between 2002 and 2004, and a greater drop in EPT than ET use. Invasive breast cancer rates decreased in all HT groups except current EPT users, whereas screening mammography rates rose in all groups other than the EPT group, and rose in the overall study population through 2006. The investigators concluded that changes in screening could not explain their observed decrease in breast cancer incidence. These results are consistent with their previous study showing a sharp decline in breast cancer incidence in women aged 50 and older between 2002 and 2005 within a population of women who continued to undergo screening mammography (7), as well as with the follow-up report of the WHI studies in which a decline in breast cancer incidence was seen in the groups of women who discontinued EPT but not in the control groups, while mammography use was similar in both groups (8).

It is likely that EPT has a dual effect on breast cancer, promoting the growth of existing cancers and inducing new cancers that would not otherwise occur. Discontinuation of EPT would quickly decrease observed breast cancer incidence by slowing the growth rate and/or causing permanent regression of subclinical cancers. Risk might still remain higher than that of nonusers over the next few years, as previously undetectable EPT-induced tumors grow to a detectable size, and as reversal of the EPT-induced increase in mammographic density unmasks previously undetected slow-growing cancers (9). Increased breast cancer risk in former EPT users compared with nonusers was observed in the WHI studies but not in the Buist study. The reported effect of ET on cancer incidence has varied from a 23% decrease in the WHI-randomized trial (10) to a 30% increase in the observational Million Women Study (11). In both the WHI and Buist studies, a decreased breast cancer incidence was observed in former ET users compared with never users. Several preclinical and clinical studies have provided a biologic rationale for this phenomenon (12).

Some of the other findings in the current Buist study warrant discussion. There was a decrease in breast cancer incidence over time among women who continued ET and

among HT nonusers, 2 groups in which no change would have been expected. Most of this decrease happened after 2007. The gradual decrease in the age of the study population, an apparent decrease in screening mammography rates at the end of the study period, or random variation due to the relatively small numbers in each subgroup, are all possible explanations.

The ability of antiestrogen chemoprevention to decrease the incidence of both ductal carcinoma *in situ* (DCIS) and invasive cancer suggests that administration or withdrawal of HT should have an effect on DCIS incidence. Surprisingly, in the randomized WHI trial of EPT, no increase in DCIS incidence was observed, nor was any decrease in the incidence of DCIS reported in 4 cancer registries between 2001 and 2003 when invasive cancer rates decreased by 13% (13). Similarly, the Buist study found similar rates of DCIS in all subgroups. However, in a larger study, the decrease in DCIS incidence was similar to the decline in invasive cancer (7). The smaller studies may have lacked that power to discern a significant change in DCIS incidence over time.

Buist and colleagues and others have now convincingly showed that the marked decline in breast cancer incidence in the United States between 2003 and 2005 (followed by stabilization at the lower level) was the direct result of the decline in the use of EPT. While this is an important piece of information in its own right, it illustrates the principle that modification of a factor that has a relatively minor effect on the breast cancer risk of an individual woman (relative risk, RR < 2) but has a high prevalence in the general population, can have a major impact on cancer incidence in that population The rapidly increasing breast cancer incidence in the developing world provides a critical window of opportunity for epidemiologists to determine the responsible lifestyle, environmental, or infectious factors. As with any other epidemic, identification and aggressive reduction of any reversible risk factors must become an immediate priority.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Received March 12, 2012; accepted March 12, 2012; published OnlineFirst March 21, 2012.

References

1. National Cancer Institute Surveillance Epidemiology and End Results. Bethesda, MD: National Cancer Institute; 2011. Available from: http://seer.cancer.gov/statfacts/html/breast.html
2. Esserman L, Shieh Y, Thompson I. Rethinking screening for breast cancer and prostate cancer. JAMA 2009;302:1685–02.
3. Buist DSM, Walker R, Bowles EJA, Carney PA, Taplin SH, Onega T, et al. Screening mammography use among current, former and never hormone therapy users may not explain recent declines in breast cancer incidence. Cancer Epidemiol Biomarkers Prev. 2012 Feb 20. [Epub ahead of print].
4. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
5. Breen N, Cronin K, Meissner HI, Taplin SH, Tangka FK, Tiro JA , et al. Reported drop in mammography: is this a cause for concern? Cancer 2007;109:2405–9.
6. Rao Vam, Levin DC, Parker L, Frangos AJ. Recent trends in mammography uitilizationin the Medicare population: is there a cause for concern? J Am Coll Radiol 2008;5:652–6.
7. Farhat GN, Walker R, Buist DS, Onega T, Kerlikowske K. Changes in invasive breast cancer and ductal carcinoma *in situ* rates in relation to the decline in hormone therapy use. J Clin Oncol 2010;28:5140–6.
8. Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. New Engl J Med 2009;360:573–87.
9. Rutter CM, Mamdelson MT, Laya MB, Taplin S. Changes in breast density associated with initiations, discontinuation and continuing use of hormone replacement therapy. JAMA 2001;285:171–6.
10. Stefanick ML, Anderson GL, Margolis KL, Hendrix SL, Rodabough RJ, Paskett ED, et al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006;295:1647–57.
11. Beral V. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–37.
12. LaCroix AZ, Chlebowski RT, Manson JE, Aragaki AK, Johnson KC, Martin L, et al. Health outcomes after stopping conjugated equine estrogens among post-menopausal women with prior hysterectomy: a randomized trial. JAMA 2011;305:1305–14.
13. Kerlikowske K, Miglioretti DL, Buist DS, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. J Natl Cancer Inst 2007;99:1335–9.