Editorial

Pregnancy-Associated Breast Cancer

An Entity Needing Refinement of the Definition

Virginia F. Borges, MD MMSc[1,2] and Pepper J. Schedin, PhD[1,2,3]

Pregnancy, as a modifier of risk for developing breast cancer, confers a "dual effect" of both increased risk followed by subsequent protection for younger mothers. Although the protective effect of pregnancy is broadly appreciated, all women, regardless of their age at first birth, have a subsequent period of years during which they are at increased risk for the development of breast cancer.[1] For first-time mothers aged 25 years or younger, the risk is modestly increased compared to nulliparous women, and in a large Norwegian cohort, has been shown to last approximate 9 years, at which time a cross-over effect occurs.[2] This cross-over effect then changes the role of pregnancy from one of breast cancer promotion to subsequent protection. For a woman who delays childbearing until age 30 to 35, the risk for breast cancer is significantly increased compared to younger mothers, and the cross-over effect is delayed until her 60s.[3] Women who wait until age >35 years for their first childbirth permanently increase their risk of breast cancer compared to nulliparous women.[4] Rather surprisingly, peak incidence of breast cancer does not occur during pregnancy or in the immediate postpartum period, but rather approximately 6 years postpartum.[3] Breast cancers diagnosed during pregnancy or within the postpartum period have been reported to present with more adverse clinical characteristics and are variably reported to have worsened breast-cancer specific outcomes for the mother. A review of these "pregnancy-associated breast cancers" was published by our group in 2009.[5]

In this issue of *Cancer*, Murphy et al[6] report a single-institution, case-controlled, retrospective study of pregnancy-associated breast cancer (PABC), where this entity is defined as cases of women diagnosed with breast cancer during pregnancy or within 1 year postpartum. Controls in this article are defined as individuals with breast cancer who are matched by age and year of diagnosis, with no prior childbirth within 12 months of breast cancer diagnosis. Stage I-III breast cancers were included, using AJCC staging criteria. Their review encompassed records from 1981 until 2007 and serves as a follow-up series to an initial publication in 1991 of their institutions' earlier 20-year experience.[7] The authors identified 99 cases meeting their definition of PABC and 186 matched controls. Of note, the age range of their PABC cases is from 24 to 48 years, with 36% diagnosed during pregnancy and 63% diagnosed postpartum at a median of 6 months since childbirth. A total of 39% of their controls are reported to be nulliparous, whereas the majority of the controls are parous with 1 to 4 births. In terms of baseline characteristics of the tumors at diagnosis, the authors identified statistically significant differences for PABC having results that were more often negative for the estrogen and progesterone receptors (59% versus 31% and 72% versus 40%, respectively) but no difference in human epidermal growth factor receptor 2 (Her2/neu) overexpression. Also, PABC was found to have a higher degree of nodal involvement and pathologic grade 3 tumors. On multivariate analysis, they did not find any significant difference in disease-free or overall survival between PABC and their controls.

The work by Murphy et al addresses the important topic of PABC and provides an excellent level of detail regarding the clinical characteristics of the breast cancers at diagnosis and the treatments received by the PABC cases. Their strategy of matching by age and year at diagnosis permits the identification of a higher degree of hormone receptor negativity, nodal involvement, and poorer grade tumors in their PABC cases, above and beyond what would be expected in a younger breast cancer cohort. Their results support the findings of earlier research.[7-9] Importantly, the researchers provide staging

Corresponding author: Virginia F. Borges, MD MMSc, Associate Professor of Medicine, Director, Young Women's Breast Cancer Translational Program, University of Colorado Anschutz Medical Campus, 12801 East 17th Avenue, MS 8117, Rm 8112, Aurora, CO 80045; Phone: (303) 724-0186; Virginia.borges@ucdenver.edu

[1]Division of Medical Oncology, University of Colorado Anschutz Medical Campus, Aurora, Colorado; [2]University of Colorado Cancer Center, Denver, Colorado; [3]AMC Cancer Research Center, Aurora, Colorado

See original referenced article on pages 3254-9, this issue.

DOI: 10.1002/cncr.26643, **Received:** September 21, 2011; **Accepted:** October 4, 2011, **Published online** November 15, 2011 in Wiley Online Library (wileyonlinelibrary.com)

data for their cases diagnosed during pregnancy versus in the 1 year postpartum to show that no stage migration occurred due to delayed diagnosis between the 2 subgroups of PABC, thus eliminating a potential confounder previously reported in PABC studies.[7,9,10]

The discussion presented by Murphy et al highlights the current understanding of our ability to effectively and safely treat breast cancer during pregnancy and the goal of prospective large registries for gaining future insight. However, in our opinion, their reported observation that the PABC cases have similar disease-free and overall survival as controls requires caution in its interpretation and specifically highlights the challenges of research in the PABC field. Significant large, global epidemiologic studies have consistently identified the postpartum period as specifically conferring an increased risk of metastasis and death. The exact length of time this increased risk persists in the postpartum period remains to be identified, but to date, the effect has been reported out to 2 and 5 years.[11-17] A very contemporary publication to the study by Murphy et al identifies higher mortality in postpartum breast cancer peaking 2 years after diagnosis and continuing until 10 years later.[18] Based on these previous studies, the criteria used to stratify cases into PABC and non-PABC by Murphy et al results in two-thirds of their controls sharing the negative prognostic effect of a prior pregnancy with the postpartum PABC cases, with recent childbirth potentially as close as 13 months postpartum included in the control group. This issue also confounds the results of a similar recent large PABC study that shows no adverse prognosis when PABC is restricted to the combination of cases diagnosed during pregnancy and early postpartum period.[19]

Research on cases diagnosed during pregnancy is further challenged given the heterogeneity with how these cases are handled clinically. In the current study, within the pregnant PABC cases, 25% underwent termination of the pregnancy (trimester not reported) followed by subsequent usual care, and therefore did not experience the full biologic impact that completion of pregnancy and the postpartum state would have on the breast, breast cancer, and/or potential microresidual disease in the host. Among the remaining pregnant cases, only 25% of the cases received chemotherapy during pregnancy, which may alter outcomes if the chemotherapy were unnecessarily delayed until completion of the pregnancy in reflection of historical practice patterns.

In summary, we highlight the difficulties in defining what is and what is not PABC. Is it defined as cases diagnosed during pregnancy, shortly after birth, less than 2 years postpartum, less than 5 years postpartum, or even later? We suggest for the future that outcomes data drive the definition of PABC. Further, given that poor prognosis persists for several years after child birth, with the length of time required for risk to return to nulliparous levels currently unknown, we propose that the appropriate control set for a pregnancy breast cancer or postpartum breast cancer study would be nulliparous women. Moreover, given the existing data from the epidemiologic literature and the emerging data from preclinical modeling that identifies the role of postpartum involution in promoting cancer proliferation and metastasis,[20] we propose that PABC be viewed as 2 distinct subsets: those cases diagnosed during pregnancy and those diagnosed in the postpartum time frame. Inclusion of these guidelines into future experimental design is anticipated to help resolve discrepancies that currently exist in the field, which could have significant impact on the health and well-being of pregnant and recently pregnant women.

REFERENCES

1. Janerich DT, Hoff MB. Evidence for a crossover in breast cancer risk factors. *Am J Epidemiol.* 1982;116:737-742.
2. Albrektsen G, Heuch I, Tretli S, Kvåle G. Breast cancer incidence before age 55 in relation to parity and age at first and last births: a prospective study of one million Norwegian women. *Epidemiology.* 1994;5:604-611.
3. Schedin P. Pregnancy-associated breast cancer and metastasis. *Nat Rev Cancer.* 2006;6:281-291.
4. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst.* 1996;88:359-364.
5. Lyons TR, Schedin PJ, Borges VF. Pregnancy and breast cancer: when they collide. *J Mammary Gland Biol Neoplasia.* 2009;14:87-98.
6. Murphy CG, Mallan D, Stein S, et al. Current or recent pregnancy is associated with adverse pathologic features but not impaired survival in early breast cancer. 2012;118:3254-3259.
7. Petrek JA, Dukoff R, Rogatko A. Prognosis of pregnancy-associated breast cancer. *Cancer.* 1991;67:869-872.
8. Middleton LP, Amin M, Gwyn K, Theriault R, Sahin A. Breast carcinoma in pregnant women: assessment of clinicopathologic and immunohistochemical features. *Cancer.* 2003;98:1055-1060.
9. Bonnier P, Romain S, Dilhuydy JM, et al. Influence of pregnancy on the outcome of breast cancer: a case-control study. Societe Francaise de Senologie et de Pathologie Mammaire Study Group. *Int J Cancer.* 1997;72:720-727.
10. Guinee VF, Olsson H, Möller T, et al. Effect of pregnancy on prognosis for young women with breast cancer. *Lancet.* 1994;343:1587-1589.
11. Rodriguez AO, Chew H, Cress R, et al. Evidence of poorer survival in pregnancy-associated breast cancer. *Obstet Gynecol.* 2008;112:71-78.

12. Whiteman MK, Hillis SD, Curtis KM, McDonald JA, Wingo PA, Marchbanks PA. Reproductive history and mortality after breast cancer diagnosis. *Obstet Gynecol.* 2004;104:146-154.
13. Stensheim H, Møller B, van Dijk T, Fosså SD. Cause-specific survival for women diagnosed with cancer during pregnancy or lactation: a registry-based cohort study. *J Clin Oncol.* 2009;27:45-51.
14. Daling JR, Malone KE, Doody DR, Anderson BO, Porter PL. The relation of reproductive factors to mortality from breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2002;11:235-241.
15. Bladström A, Anderson H, Olsson H. Worse survival in breast cancer among women with recent childbirth: results from a Swedish population-based register study. *Clin Breast Cancer.* 2003;4:280-285.
16. Dodds L, Fell DB, Joseph KS, et al. Relationship of time since childbirth and other pregnancy factors to premenopausal breast cancer prognosis. *Obstet Gynecol.* 2008;111: 1167-1173.
17. Phillips KA, Milne RL, West DW, et al. Prediagnosis reproductive factors and all-cause mortality for women with breast cancer in the breast cancer family registry. *Cancer Epidemiol Biomarkers Prev.* 2009;18:1792-1797.
18. Johansson AL, Andersson TM, Hsieh CC, Cnattingius S, Lambe M. Increased mortality in women with breast cancer detected during pregnancy and different periods postpartum. *Cancer Epidemiol Biomarkers Prev.* 2011;20:1865-1872.
19. Beadle BM, Woodward WA, Middleton LP, et al. The impact of pregnancy on breast cancer outcomes in women-or=35 years. *Cancer.* 2009;115:1174-1184.
20. Lyons TR, O'Brien J, Borges VF, et al. Postpartum mammary gland involution drives progression of ductal carcinoma in situ through collagen and COX-2. *Nat Med.* 2011;17:1109-1115.