

Importance of Smoking Cessation to Reduce Breast Cancer Mortality

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In 2014, the Surgeon General concluded that, among breast cancer survivors, persistent cigarette smoking was causally associated with adverse health outcomes, although the evidence for an association with breast cancer recurrence was only suggestive.¹ Published associations with recurrence could not rule out potential confounders. For example, smokers were known to have lower rates of mammographic screening, which suggested that they might be diagnosed with higher-stage disease, which could explain a worse prognosis.¹ Smokers were more likely to have developed comorbidities that affected longevity; some also received less than recommended doses of cancer treatments, including adjuvant endocrine therapies for patients with hormone receptor–positive disease.¹

Recently, reports from breast cancer–specific longitudinal studies have addressed these concerns. One issue that has limited the ability to detect a relationship between smoking and breast cancer prognosis is the low prevalence of ongoing smoking among patients diagnosed with breast cancer.² The low prevalence of persistent smoking requires a large sample size of breast cancer survivors to identify moderate risk associations. Two recent studies, each with approximately 3,000 breast cancer survivors, did not have the power to achieve statistical significance for an estimated 23% increased risk of breast cancer mortality.^{2,3} A lack of power was also a problem for a hospital-based cohort of nearly 6,000 breast cancer survivors, in whom the estimated smoking effect size was +15%.⁴ However, when the effect size was considerably larger (eg, +55%), a smaller follow-up study of approximately 2,000 breast cancer survivors reported the effect as statistically significant.⁵

In the article that accompanies this editorial, a study by Passarelli et al⁶ reported results from a well-powered study of 20,691 breast cancer survivors, in which persistent smoking was associated with a statistically significant 25% increased risk of breast cancer death after analysis was controlled for stage and multiple risk factors. This is one of a number of recently published studies (with various study designs) to report a statistically significant association of persistent smoking with breast cancer–specific outcomes. One study was a cohort of almost 10,000 breast cancer survivors that identified an effect size of 61%.⁷ Two large population-based cohorts have reported an association of smoking with breast cancer mortality: one was a study of 128,000 breast cancer survivors in Florida, which reported an effect size of +15%;⁸ the other was a study of > 300,000 Norwegian breast cancer survivors that reported an effect size of +33%.⁹ In a large study

that included > 6,000 patients with hormone receptor–positive breast cancer who had survived for at least 5 years, Nechuta et al¹⁰ noted that, after analysis was adjusted for other risk factors that included non–smoking-related lifestyle measures, persistent smoking was associated with a +30% increase in breast cancer mortality.

The consistency of the statistically significant associations that link persistent smoking with higher breast cancer mortality across these studies suggests a causal association. The recent study by Passarelli et al⁶ observed that patients who quit smoking had a 33% reduction in breast cancer death rate; however, because these patients were a small subsample of those enrolled in the overall study, this result did not reach statistical significance. Both the magnitude and the direction of the effect, though, are consistent with other evidence of the benefits of smoking cessation for other cancers.¹

We estimate that up to 20,000 US women will continue smoking after a diagnosis of breast cancer. The evidence described in this editorial suggests that successful promotion of smoking cessation among these patients could lead to a significant, additive benefit to the established benefits of adjuvant chemotherapy,¹¹ adjuvant endocrine therapy,¹² and postmastectomy radiation therapy¹³ and that it may be as important as, or more important than, any other survivorship recommendations. Additionally, smoking cessation in these patients may mitigate surgical complications¹⁴ and avoid much of the excess risk of secondary lung cancer and heart disease seen in patients with breast cancer who smoke and who undergo curative intent radiation.¹⁵

Reasons why approximately half of medical oncologists have not aggressively promoted smoking cessation¹⁶ include the following: unclear evidence of benefit; lack of time; priority of primary treatment; and inadequate training and expertise, especially when patients exhibit high psychological stress and depression. From the study by Passarelli et al,⁶ we can calculate that approximately 45% of smokers (352 of 786) at the time of breast cancer diagnosis may successfully quit within 6 years. This cessation rate is similar to the 43% reported for smokers diagnosed with cancers strongly related to smoking, such as head, neck, and lung cancers.¹⁷ With this additional evidence of mortality benefit, it is appropriate to revisit the resources necessary for promoting smoking cessation in breast oncology practice and for collecting data in future research studies. It should be possible to increase the cessation rate among patients with breast cancer to 75%. The new National Comprehensive Cancer Network Guidelines for Smoking

Cessation¹⁶ outline how this might be achieved: appropriate assessment of smoking status at each visit, provider recommendation of evidence-based pharmacologic and behavioral therapy to assist in the cessation attempt, and close follow-up of this issue at subsequent visits.

Enhanced focus on smoking in breast cancer clinical research and enhanced resources for smoking cessation in clinical practice are needed. In 2012, a study by Peters et al¹⁸ reported that < 22% of randomized cancer trials included a measure of current smoking status. Failure to incorporate standardized tobacco assessments into breast cancer studies at each assessment point will limit analysis of this important risk factor for recurrence and could potentially confound the results of the study. Collection of smoking status should be a priority for future breast cancer studies, given the modest costs and the importance of this risk factor in outcomes.

The report by Passarelli et al⁶ suggests that now is the time to promote research on smoking cessation in patients with breast cancer and, most important, to prescribe and promote smoking cessation at each visit to minimize treatment complications and maximize breast cancer survival and overall health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress—A Report of the Surgeon General. Atlanta, GA, US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014
2. Saquib N, Stefanick ML, Natarajan L, et al: Mortality risk in former smokers with breast cancer: Pack-years vs. smoking status. *Int J Cancer* 133:2493-2497, 2013
3. Seibold P, Vrieling A, Heinz J, et al: Pre-diagnostic smoking behaviour and poorer prognosis in a German breast cancer patient cohort: Differential effects by tumour subtype, NAT2 status, BMI, and alcohol intake. *Cancer Epidemiol* 38:419-426, 2014
4. Bérubé S, Lemieux J, Moore L, et al: Smoking at time of diagnosis and breast cancer-specific survival: New findings and systematic review with meta-analysis. *Breast Cancer Res* 16:R42, 2014
5. Boone SD, Baumgartner KB, Baumgartner RN, et al: Active and passive cigarette smoking and mortality among Hispanic and non-Hispanic white women diagnosed with invasive breast cancer. *Ann Epidemiol* 25:824-831, 2015
6. Passarelli MN, Newcomb PA, Hampton JM, et al: Cigarette smoking before and after breast cancer diagnosis: Mortality from breast cancer and smoking-related diseases. *J Clin Oncol* doi:10.1200/JCO.2015.63.9328
7. Pierce JP, Patterson RE, Senger CM, et al: Lifetime cigarette smoking and breast cancer prognosis in the After Breast Cancer Pooling Project. *J Natl Cancer Inst* 106:djt359, 2015
8. Padron-Monedero A, Tannenbaum SL, Koru-Sengul T, et al: Smoking and survival in female breast cancer patients. *Breast Cancer Res Treat* 150:395-403, 2015
9. Bjerkaas E, Parajuli R, Engeland A, et al: The association between lifetime smoking exposure and breast cancer mortality: Results from a Norwegian cohort. *Cancer Med* 3:1448-1457, 2014
10. Nechuta S, Chen WY, Cai H, et al: A pooled analysis of post-diagnosis lifestyle factors in association with late estrogen-receptor positive breast cancer prognosis. *Int J Cancer* doi:10.1002/ijc.29940 [epub ahead of print on December 9, 2015]
11. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Peto R, Davies C, et al: Comparisons between different polychemotherapy regimens for early breast cancer: Meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 379:432-444, 2012
12. Early Breast Cancer Trialists' Collaborative Group, Dowsett M, Forbes JF, et al: Aromatase inhibitors versus tamoxifen in early breast cancer: Patient-level meta-analysis of the randomised trials. *Lancet* 386:1341-1352, 2015
13. Early Breast Cancer Trialists' Collaborative Group, McGale P, Taylor C, et al: Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: Meta-analysis of individual patient data for 8135 women in 22 randomised trials. *Lancet* 383:2127-2135, 2014
14. Tang R, Coopey SB, Colwell AS, et al: Nipple-sparing mastectomy in irradiated breasts: Selecting patients to minimize complications. *Ann Surg Oncol* 22:3331-3337, 2015
15. Taylor C, Correa C, Anderson S, et al: Late side effects of breast cancer radiotherapy: Second cancer incidence and non-breast-cancer mortality among 40,000 women in 75 trials. 38th Breast Cancer Symposium, San Antonio, TX, December 8-12, 2015 (abstr)
16. Shields PG: New NCCN Guidelines: Smoking cessation for patients with cancer. *J Natl Compr Canc Netw* 13:643-645, 2015 (suppl)
17. Burris JL, Studts JL, DeRosa AP, et al: Systematic review of tobacco use after lung or head/neck cancer diagnosis: Results and recommendations for future research. *Cancer Epidemiol Biomarkers Prev* 24:1450-1461, 2015
18. Peters EN, Torres E, Toll BA, et al: Tobacco assessment in actively accruing National Cancer Institute Cooperative Group Program clinical trials. *J Clin Oncol* 30:2869-2875, 2012

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