The Sin of Exclusion: Applicability of Trials Encouraging Omission of Radiation Therapy to Nonwhite Patients With Breast Cancer

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Over the past decade, there has been a wave of high-quality evidence supporting omission of radiation therapy (RT) for early-stage breast cancer.[1-3] The arguments have centered around the absence of a survival benefit with RT over best medical therapy, which has made the argument for omitting RT persuasive, particularly for elderly patients whose expected lifespan does not typically justify the long-term benefits of RT over the shorter-term risks.[1-3] The most prominent recent trials have been the Cancer and Leukemia Group B (CALGB) 9343 trial (studying women age ≥70 years with estrogen receptor–positive [ER+], clinical stage I breast cancer), the Postoperative Radiotherapy in Minimum Risk Elderly (PRIME) II trial (studying women age ≥ 65 years with ER+ tumors ≤ 3 cm), and the Austrian Breast and Colorectal Cancer Study Group (ABCSG) Study 8A (women with tumors < 3 cm, ER or progesterone receptor positive, and negative lymph nodes were studied).[1-3]

These trials have built upon the foundation of older trials such as the National Surgical Adjuvant Breast and Bowel Project B-21 trial[4] (studying women with ER+ tumors ≤ 1 cm regardless of age) and Fyles et al.[5] (studying woman age ≥ 50 with ER+ tumors up to 4 cm), which were among the first to assess the necessity for RT in early-stage breast cancer for appropriately selected patients.

An unexplored aspect of these recent seminal trials is their applicability to patients regardless of race or ethnicity, particularly regarding nonwhite patient representation commensurate with their demographic distribution in the United States and the United Kingdom, respectively[1-3,6,7] (Table 1). Although the typical socioeconomic profile of a patient likely to receive RT favors white patients, this should not result in the obfuscation of nonwhite patients from consideration when interpreting the relevance of these trials to these populations. Although genetic differences in tumor behavior by race have been documented, often manifesting as more aggressive tumor biology in underrepresented minorities, data demonstrating racial differences in outcomes despite similar access to optimal care are largely lacking.[8-11]

PRIME II and ABCSG 8A originated in the United Kingdom and Austria, respectively, where there are no federal mandates requiring representative portions of minorities to be included in high-quality clinical trials; in fact, neither study even reported the racial and ethnic demographics of their combined 2,195 patients.[2,3] The same excuse cannot be made for studies originating in the United States (such as CALGB 9343), where the National Institutes of Health (NIH) Revitalization Act of 1993 has required that members of minority populations be adequately represented in

DOI: https://doi.org/10.1200/JOP.18.00344

Table 1. Recent Studies Providing Level 1 Evidence Supporting Omission of Radiation Therapy for Early-Stage Breast Cancer and Their Representation (Percentage) by Race and Ethnicity Compared With the US population as Defined by the 2010 US Census and the UK Population as Defined by the 2011 UK Census

Race/Ethnicity	US Census (2010)[6]	CALGB 9343 A (2013)[1]	UK Census (2011)[7]	PRIME II (2015)[2]	ABCSG 8A (2007)[3]
White	72.4	90.3	87.1	NR	NR
Black	12.6	7.1	3.0	NR	NR
Hispanic*	16.3	2.0	NR	NR	NR
Asian	4.8	0.3	6.9	NR	NR
American Indian	0.9	< 0.4 (NR)	NR	NR	NR
Total population, no.	308,745,538	636	63,182,178	1,326	869
Nation of origin	US	US	UK	UK	Austria
Cancer type	All	Breast	All	Breast	Breast
Median follow-up	—	12.6 years	—	5 years	53.8 months

NOTE. Data given as % unless otherwise indicated.
Abbreviations: —, not applicable; NR, not reported; UK, United Kingdom.
*Stratified in the US Census by ethnicity, which depicts Hispanic versus non-Hispanic people.

clinical research.[1,12] The failure of US trials to approximate this standard has sadly not changed since the 20th century; the proportion of underrepresented minority patients in phase III cancer treatment and prevention clinical trials has actually decreased from 1990 to 2010.[12,13] Specifically, the proportion of black patients in phase III cancer treatment and prevention trials decreased from 10.5% (1990 to 2000) to 6.2% (2000 to 2010), compared with their actual representation in the US population of 11.7% in 1990 and 12.6% in 2010.[6,13] Unfortunately, clinical trials with even larger numbers of accrued patients often do not report patient racial and ethnic demographics, such as the ongoing Trial Assigning Individualized Options for Treatment (TAILORx) trial, which contains more than 10,200 participants and has been touted as the largest adjuvant breast cancer treatment trial ever conducted.[14] It would be wise for the NIH to revisit and modify its original mandate to optimally address this issue.

The fact that trials such as CALGB 9343, ABCSG 8A, and PRIME II have been widely accepted as applicable to all patients regardless of the racial and ethnic distributions in their makeup is a testament to how ineffective the NIH mandate has been in adequately representing people of color (Table 1), who remain markedly underrepresented in high-quality trials.[13-15] The direct advertisement of the CALGB results by organizations such as the Susan G. Komen Foundation without comment on this issue of representation is an example (Fig 1). There may be some mitigating factors for early-stage breast cancer (ie, the potential for racial differences in screening behaviors to result in fewer early breast cancers diagnosed in nonwhite patients $\geq$ 70 years compared with older white patients); however, the overall inattentiveness of these trials to nonwhite patients remains disturbing, even if some of this inattentiveness could theoretically be attributable to the reticence of nonwhite patients risking subjection to malicious, unethical clinical studies in the vein of the Tuskegee Syphilis Study, which concluded (only because of whistleblower activity) less than 25 years before CALGB 9343 enrollment began.

The reality of this observation can become a double-edged sword: For nonwhite patients, particularly underrepresented minorities meeting criteria for RT omission, can we legitimately base a decision not to treat them on results of these studies? Do we use this information to justify potentially overtreating minority patients? Or do we continue with business as usual, pretending that these studies adequately reflect and represent these patient populations, even though they clearly do not? There is no clear right answer, but it is apparent from the sworn oath we took when we became physicians that the wrong approach is to counsel nonwhite patients without addressing this issue, thereby impairing their ability to make the most informed medical decision possible.

Additional clinical work is needed to validate the results of these studies when applied to real-world populations, which

Fig 1. Direct advertisement of CALGB 9343 study results shortly after publication on the Susan G. Komen Foundation website.

consist of dramatically more nonwhite patients than in any of these three randomized trials. Only then will the medical community be able to apply actual evidence to the current assumption that the level 1 evidentiary support of RT omission provided by CALGB 9343, ABCSG 8A, and PRIME II is applicable to nonwhite patients. Furthermore, a reversal of the disturbing decade-long trend of disproportionate scarcity of funding for RT trials compared with other oncological clinical trials would greatly aid in improving the applicability of these trials to nonwhite patients.[16] Powering of future trials for subset analyses from the onset would increase accrual of nonwhite patients and establish the applicability of these trials to underrepresented minorities, who may have different tumor biology from white patients. Such powering would also highlight the dearth of representation of minorities, as it would undoubtedly cause delays in trial onset unless trial

investigators redoubled their efforts to actively recruit minority patients into their studies. Linking the dearth of minority participation in clinical trials to the professional and financial reputation associated with timely physician completion of trials may provide an incentive to address this problem, which, to our knowledge, has been previously unexplored. The relative failure of programs such as the minority-based centers of the National Cancer Institute Community Oncology Research Program to improve the dearth of minority-patient representation in clinical trials indicates the complexity of this problem, which requires multifarious and innovative solutions. Given the present dearth of minorities in clinical trials, a potential solution could involve increased use of registry data, claims data, and aggregators of electronic medical record data. Although these sets have significant limitations (ie, the lack of reliable recurrence data in the National Cancer Database and SEER), their superior inclusion of minorities may help fill the representation gap until clinical trials have progressed to the point where minorities are adequately represented.

In our view, the optimal philosophy of a physician facing these situations will mirror the immortal words of an influential human rights activist: "I'm for truth, no matter who tells it. I'm for justice, no matter who it is for or against. I'm a human being, first and foremost, and as such I'm for whoever and whatever benefits humanity as a whole."[17] JOP

Authors' Disclosures of Potential Conflicts of Interest
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References

1. Hughes KS, Schnaper LA, Bellon JR, et al: Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. J Clin Oncol 31:2382-2387, 2013

2. Kunkler IH, Williams LJ, Jack WJ, et al: Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. Lancet Oncol 16:266-273, 2015

3. Pötter R, Gnant M, Kwasny W, et al: Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. Int J Radiat Oncol Biol Phys 68:334-340, 2007

4. Fisher B, Bryant J, Dignam JJ, et al: Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in women with invasive breast cancers of one centimeter or less. J Clin Oncol 20:4141-4149, 2002

5. Fyles AW, McCready DR, Manchul LA, et al: Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 351:963-970, 2004

6. US Census Bureau: Overview of race and Hispanic origin: 2010. https://www.census.gov/prod/cen2010/briefs/c2010br-02.pdf.

7. Office for National Statistics: 2011 Census: Ethnic group, local authorities in the United Kingdom. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/keystatisticsandquickstatisticsforlocalauthoritiesintheunitedkingdom/2013-10-11

8. McClelland S III, Deville C, Thomas CR Jr, et al: An overview of disparities research in access to radiation oncology care. J Radiat Oncol 5:437-444, 2016

9. Amend K, Hicks D, Ambrosone CB: Breast cancer in African-American women: Differences in tumor biology from European-American women. Cancer Res 66:8327-8330, 2006

10. Cunningham JE, Walters CA, Hill EG, et al: Mind the gap: Racial differences in breast cancer incidence and biologic phenotype, but not stage, among low-income women participating in a government-funded screening program. Breast Cancer Res Treat 137:589-598, 2013

11. O'Brien KM, Cole SR, Tse CK, et al: Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Res 16:6100-6110, 2010

12. Hamel LM, Penner LA, Albrecht TL, et al: Barriers to clinical trial enrollment in racial and ethnic minority patients with cancer. Cancer Contr 23:327-337, 2016

13. Kwiatkowski K, Coe K, Bailar JC, et al: Inclusion of minorities and women in cancer clinical trials, a decade later: Have we improved? Cancer 119:2956-2963, 2013

14. Sparano JA, Gray RJ, Makower DF, et al: Prospective validation of a 21-gene expression assay in breast cancer. N Engl J Med 373:2005-2014, 2015

15. McClelland S III, Mitin T: The danger of applying the ProtecT trial to minority populations. JAMA Oncol 4:291, 2018

16. Liu X, Zhang Y, Tang LL, et al: Characteristics of radiotherapy trials compared with other oncological clinical trials in the past 10 years. JAMA Oncol 4:1073-1079, 2018

17. X M, Haley A, Shabazz A: The Autobiography of Malcolm X. New York, NY, Grove Press, 1965.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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