Editorial Commentary

Biological features and locoregional recurrence in early-onset breast cancer: insights from the Young Women's Breast Cancer Study and the Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer

Wilson Cheah^, Robert Stuart Kemp^, Ellen Roxane Copson^, Ramsey Ian Cutress^

School of Cancer Sciences, Faculty of Medicine, University of Southampton and University Hospitals Southampton, Southampton, UK

Correspondence to: Ramsey Ian Cutress, BM BCh, BA, PhD. School of Cancer Sciences, Faculty of Medicine, University of Southampton and University Hospitals Southampton, Cancer Sciences, Somers Building, Southampton General Hospital, Southampton, SO16 6YD, UK. Email: R.I.Cutress@soton.ac.uk.

Comment on: Dominici LS, Zheng Y, King TA, *et al.* Long-Term Locoregional Outcomes in a Contemporary Cohort of Young Women With Breast Cancer. JAMA Surg 2025;160:964-71.

Keywords: Mastectomy; locoregional recurrence (LRR); breast-conserving therapy (BCT); early-onset breast cancer (EOBC); Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH)

Submitted Dec 15, 2025. Accepted for publication Jan 20, 2026. Published online Feb 05, 2026.

doi: 10.21037/gs-2025-1-578

View this article at: https://dx.doi.org/10.21037/gs-2025-1-578

Early-onset breast cancer (EOBC) is defined as breast cancer diagnosed before the age of 40 (1). EOBC is relatively rare, accounting for only 5–7% of all breast cancer cases in high-income countries, although reports indicate its incidence may now be increasing in several of these (2,3). In contrast, in low- and middle-income countries where the population age structure and screening patterns differ, premenopausal breast cancer, including EOBC, represents a significant burden, accounting for an estimated 55% of all breast cancer cases (2,4,5). Importantly, EOBC remains a leading cause of death among young women under 40 years old worldwide (6,7).

Compared to breast cancers diagnosed in postmenopausal women, EOBC is often characterised by less favourable disease features, irrespective of stage at presentation. Women with EOBC are more likely to present with histological markers of poor prognosis, including with larger tumours, tumours of higher histological grade, lymphovascular invasion and aggressive molecular subtype including triple-negative (8,9). EOBC is also associated with a higher incidence of local recurrence, contralateral disease and distant metastasis than breast cancer in postmenopausal women (10-12). These features suggest that EOBC may represent a biologically differing entity, rather than simply an age-defined subgroup. Furthermore, the prevalence of germline pathogenic variants (GPVs) in *BRCA1/2* and other breast cancer-predisposing genes are higher among women with EOBC compared to postmenopausal women, which may contribute to an increased risk of further in breast events, although there is no conclusive evidence that this translates into poorer overall survival or increased risk of distant disease-free survival in EOBC (13,14).

These distinctions, particularly regarding locoregional recurrences (LRRs), raise important questions about the applicability of data derived mainly from older breast cancer populations, especially in relation to the efficacy of breast-conserving therapy (BCT), which is now the standard treatment for women with early-stage invasive

^ ORCID: Wilson Cheah, 0000-0003-1170-6810; Robert Stuart Kemp, 0000-0001-6189-9273; Ellen Roxane Copson, 0000-0001-8994-4056; Ramsey Ian Cutress, 0000-0002-1719-7255.

breast cancer. Although long-term studies in predominantly postmenopausal cohorts demonstrate equivalent recurrence and survival outcomes between BCT and mastectomy (15-17), evidence remains limited to confirm whether these findings extend to women with EOBC, given their potentially distinct tumour biology and higher risk of LRR. Notably, many earlier studies reporting higher rates of LRR following BCT compared with mastectomy in EOBC predate the modern treatment era (18-20), including the use of neoadjuvant chemotherapy, platinum-based regimens, human epidermal growth factor receptor 2 (HER2)-targeted therapy, as well as more recent advances such as immunotherapy, Cyclin-Dependent Kinase 4/6 (CDK4/6) and polyadenosine-diphosphate-ribose polymerase (PARP) inhibitors. These advances may collectively contribute to lower LRR rates, which have reduced with time, regardless of surgical approach.

Recently published data from the Young Women's Breast Cancer Study (YWS), reported by Dominici *et al*. (21), provide timely evidence addressing this question by examining long-term locoregional outcomes in a modern cohort of 1,135 women diagnosed with stage I–III breast cancer at age 40 years or younger, treated between 2006 and 2016. They reported a relatively low rate of isolated LRR (5.6%) at a median follow-up of 10.1 years, comprising 5.2% local and 0.4% regional recurrences. No significant differences in LRR were observed between locoregional treatment type within molecular subtypes, consistent with broader breast cancer data suggesting that tumour biology may have a greater influence on recurrence than surgical approach (22).

It is interesting to compare these findings with those of the United Kingdom (UK) Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer (POSH), one of the largest prospective cohort studies of EOBC to date, which provides important insights into the natural history and outcomes of EOBC prior to the widespread use of contemporary systemic therapies. Maishman *et al.* reported significantly higher local recurrence rates following BCT compared with mastectomy at 5 years (5.3% *vs.* 2.6%, P<0.001) and 10 years (11.7% *vs.* 4.9%, P<0.001) (23). In contrast, Dominici *et al.* observed no significant difference in the cumulative incidence of LRR between BCT and mastectomy (without chest wall radiotherapy) at 5 years (2.9% *vs.* 3.7%) and 10 years (6.7 % *vs.* 6.5%). The cumulative incidence of LRR after mastectomy with radiotherapy in the YWS study was 1.9% at 5 years and 2.4% at 10 years. Additionally, in the POSH study, multivariable analysis showed that oestrogen receptor (ER) and HER2 status were not independent predictors of LRR, although the confidence intervals were wide and longer follow-up is warranted. Similar findings were observed in YWS.

Despite differences in recruitment catchment [United States of America (USA) for YWS and UK for POSH] and enrolment periods (YWS 2006–2016 and POSH 2000–2008), the baseline characteristics of the YWS and POSH cohorts are remarkably similar. In both studies, more than half of participants were aged 36 to 40 years, reflecting the typical age distribution of EOBC. Both cohorts also consisted predominantly of White participants (84.5% in YWS and 92.4% in POSH), which may limit the generalisability of their findings to more ethnically diverse contemporary breast cancer populations.

Tumour characteristics were likewise comparable between cohorts. Tumour stage distribution was similar, with T1 (49.6% in YWS *vs.* 48.2% in POSH), T2 (38.2% *vs.* 39.8%), T3 (10.6% *vs.* 6.2%), and T4 (1.3% *vs.* 0.2%) disease showing closely matched patterns. Pathological nodal involvement was slightly lower in YWS than in POSH (45.2% *vs.* 51.2%), which may reflect differences in the use of neoadjuvant chemotherapy. Histological grade closely mirrored between cohorts: grade 1 (6.5% in YWS *vs.* 5.7% in POSH), grade 2 (33.7% *vs.* 33.7%) and grade 3 (59.0% *vs.* 60.6%). The distribution of histological tumour subtypes in the two cohorts was similar as well, with triple-negative (17.7% *vs.* 20.4%), HER2-positive (28.3% *vs.* 27.3%), and ER-positive (73.7% *vs.* 66.0%) disease. Overall, these comparisons indicate that the superior locoregional outcomes observed in the YWS cohort are unlikely to be due to differences in baseline tumour characteristics, and may instead result from advances in systemic and locoregional management that have occurred with time.

Indeed, a higher percentage of patients in the YWS cohort received neoadjuvant chemotherapy compared with POSH (28.1% *vs.* 15.5%), as well as higher rates of HER2-targeted therapy (92.2% *vs.* 12.5%) and endocrine therapy (75.8% *vs.* 63.3%) use. It should be noted that recommendations for adjuvant systemic therapy evolved over the course of the POSH study period, with adjuvant trastuzumab for HER2-positive breast cancer becoming routinely available in the UK only from 2006, after the majority of recruitment was completed. The markedly lower use of HER2-targeted therapy in POSH therefore reflects treatment guidelines and availability at the time.

Interestingly, the mastectomy rate in the YWS cohort was significantly higher (69.0%), with a substantial

proportion being bilateral mastectomies (42.9%). In contrast, the POSH cohort had a lower overall mastectomy rate (50.2%), with only 3.9% undergoing immediate bilateral mastectomy. This difference is notable despite the majority of tumours being T1–2 stage (87.8% in YWS and 88.0% in POSH) and YWS representing a relatively more modern cohort. A considerable proportion of patients in the YWS cohort who underwent mastectomy also received post-mastectomy chest wall radiotherapy (37.5%), despite only 1.3% having T4 disease, reflecting a modern comprehensive approach to locoregional control in this high-risk cohort.

The relatively high rate of bilateral mastectomy in the YWS cohort, despite the low expected incidence of bilateral breast cancers at presentation (less than 1% in POSH), may be partly explained by differences in access to germline genetic testing. During the POSH study period, clinical genetic testing rates were low, whereas in YWS, genetic testing for inherited GPVs was more widespread, with 86.4% of participants undergoing testing and 11.5% testing positive for a *BRCA1/2* GPV. Notably, the percentage of *BRCA1/2* GPV carriers in POSH was relatively similar to the YWS cohort at 12.3%. However, genetic testing in POSH was conducted as part of the research protocol, and participants may or may not have undergone clinical genetic testing. Importantly, the results of the research-based genetic testing in POSH were not directly disclosed to participants, limiting its influence on surgical decision-making.

Broader access to genetic testing for inherited GPV, particularly *BRCA1/2* mutations, can influence surgical decision-making due to the associated risk of contralateral breast cancer. Although *BRCA* mutation carrier status was available in the study reported by Dominici *et al.*, LRR analyses were not stratified by carrier status. Further analysis stratified by *BRCA* carrier status would be valuable to determine whether outcomes differed between carriers and non-carriers. Notably, data from a contemporary cohort of *BRCA* GPV carriers showed no significant difference in local recurrence or overall survival between BCT and mastectomy after a median follow-up of 7.9 years (24). A higher incidence of contralateral breast cancer was observed among those undergoing unilateral breast surgery however, although the median age of women in that cohort was 44 years.

The comparison between the study by Dominici *et al.* and POSH highlights the significant progress in locoregional control among young women with EOBC. Advances in systemic therapy, precision radiotherapy techniques and broader indications for radiotherapy have substantially reduced LRR in EOBC, challenging the long-standing perception that BCT provides inferior local control in this high-risk population. However, paradoxically, mastectomy rates, particularly bilateral mastectomy, remain high as shown in the YWS cohort. This indicates that surgical decisions in EOBC are influenced by factors beyond oncological risk, including increased access to germline testing, perceived recurrence risk among clinicians and patients, reconstructive options, and psychological well-being (25-27). While radiotherapy remains an essential treatment modality in locoregional management, its potential long-term adverse effects warrant consideration, particularly in younger women (27,28). As clinical outcomes continue to improve, locoregional treatment planning for EOBC should integrate survivorship and psychosocial considerations, including body image and overall quality of life.

Future work should focus on continued follow-up of EOBC cohorts, as the risk of ER-positive breast cancer recurrence can occur steadily for up to 20 years (29). The higher prevalence of GPV in breast cancer-predisposing genes among women with EOBC compared to postmenopausal women makes late second primary breast cancers a particular consideration. Stratifying LRR analyses by GPV status will provide valuable insights into the efficacy of contemporary treatments and help guide a more individualised approach to locoregional management for this high-risk subgroup. Additionally, future cohorts should prioritise the inclusion of more ethnically diverse and underrepresented populations, where outcomes are often worse, to ensure the relevance and generalisability of findings.

In conclusion, the study reported by Dominici *et al.* represents a significant advance in understanding locoregional outcomes in EOBC within the context of contemporary multidisciplinary care. Its large, well-characterised cohort and long-term follow-up provide valuable reassurance that excellent locoregional control can be achieved with modern treatment strategies, including BCT, across tumour subtypes. By contextualising its findings alongside other prospective cohorts such as POSH, the study demonstrates the considerable progress in systemic and locoregional therapy for young women with EOBC and reinforces the importance of continued long-term prospective research in this unique and important population.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article did not undergo external peer review.

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-2025-1-578/coif). E.R.C. and R.I.C. declare a research grant from AstraZeneca to institution for extended follow-up of POSH. E.R.C. has received an educational grant to UK Breast Cancer Trainees Research Collaboration Group. E.R.C. receives consulting fees from Pfizer; payment or honoraria from AstraZeneca, Lilly, Pfizer, Novartis, Menarini Stemline, Roche and Guardant; and support for travel from Novartis and Roche. E.R.C. participates on monitoring or advisory board for AstraZeneca, Guardant, Lilly, Novartis, Pfizer and Roche; and has a leadership role in the World Cancer Research Fund. E.R.C. and R.I.C. receive research equipment from SECA. E.R.C. has a research collaboration with Proteotype. R.I.C. has leadership roles as breast cancer topic advisor for NICE (National Institute for Health and Care Excellence) and member of the clinical practice and standards committee for the Association of Breast Surgery. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Paluch-Shimon S, Cardoso F, Partridge AH, et al. ESO-ESMO fifth international consensus guidelines for breast cancer in young women (BCY5). Ann Oncol 2022;33:1097-118.
2. Heer E, Harper A, Escandor N, et al. Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study. Lancet Glob Health 2020;8:e1027-37.
3. DeSantis CE, Ma J, Jemal A. Trends in stage at diagnosis for young breast cancer patients in the United States. Breast Cancer Res Treat 2019;173:743-7.
4. Joko-Fru WY, Jedy-Agba E, Korir A, et al. The evolving epidemic of breast cancer in sub-Saharan Africa: Results from the African Cancer Registry Network. Int J Cancer 2020;147:2131-41.
5. McDonald JA, Rao R, Gibbons M, et al. Symposium report: breast cancer in India-trends, environmental exposures and clinical implications. Cancer Causes Control 2021;32:567-75.
6. Deaths registered in England and Wales: 2022. [cited 15 December, 2023]. Available online: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2022#cite-this-statistical-bulletin
7. Knaul FM, Bhadelia A, Gralow J, et al. Meeting the emerging challenge of breast and cervical cancer in low- and middle-income countries. Int J Gynaecol Obstet 2012;119 Suppl 1:S85-8.
8. Colleoni M, Rotmensz N, Robertson C, et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. Ann Oncol 2002;13:273-9.
9. Anders CK, Johnson R, Litton J, et al. Breast cancer before age 40 years. Semin Oncol 2009;36:237-49.
10. Zhu JW, Charkhchi P, Adekunte S, et al. What Is Known about Breast Cancer in Young Women? Cancers (Basel) 2023;15:1917.
11. Gnerlich JL, Deshpande AD, Jeffe DB, et al. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. J Am Coll Surg 2009;208:341-7.
12. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: a 25-year follow-up. Int J Radiat Oncol Biol Phys 1989;17:719-25.
13. Rosenberg SM, Ruddy KJ, Tamimi RM, et al. BRCA1 and BRCA2 Mutation Testing in Young Women With Breast Cancer. JAMA Oncol 2016;2:730-6.
14. Copson ER, Maishman TC, Tapper WJ, et al. Germline BRCA mutation and outcome in young-onset breast

cancer (POSH): a prospective cohort study. Lancet Oncol 2018;19:169-80.
15. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst 2000;92:1143-50.
16. Darby S, McGale P, Correa C, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
17. Litière S, Werutsky G, Fentiman IS, et al. Breast conserving therapy versus mastectomy for stage I-II breast cancer: 20 year follow-up of the EORTC 10801 phase 3 randomised trial. Lancet Oncol 2012;13:412-9.
18. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. Cancer 2004;100:688-93.
19. de Bock GH, van der Hage JA, Putter H, et al. Isolated loco-regional recurrence of breast cancer is more common in young patients and following breast conserving therapy: long-term results of European Organisation for Research and Treatment of Cancer studies. Eur J Cancer 2006;42:351-6.
20. van der Sangen MJ, van de Wiel FM, Poortmans PM, et al. Are breast conservation and mastectomy equally effective in the treatment of young women with early breast cancer? Long-term results of a population-based cohort of 1,451 patients aged ≤ 40 years. Breast Cancer Res Treat 2011;127:207-15.
21. Dominici LS, Zheng Y, King TA, et al. Long-Term Locoregional Outcomes in a Contemporary Cohort of Young Women With Breast Cancer. JAMA Surg 2025;160:964-71.
22. Morrow M. Personalizing extent of breast cancer surgery according to molecular subtypes. Breast 2013;22 Suppl 2:S106-9.
23. Maishman T, Cutress RI, Hernandez A, et al. Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer: The POSH Observational Cohort Study. Ann Surg 2017;266:165-72.
24. Shubeck S, Sevilimedu V, Berger E, et al. Comparison of Outcomes Between BRCA Pathogenic Variant Carriers Undergoing Breast-Conserving Surgery Versus Mastectomy. Ann Surg Oncol 2022;29:4706-13.
25. Ain Q, Richardson C, Mutebi M, et al. Does mainstream BRCA testing affect surgical decision-making in newly-diagnosed breast cancer patients? Breast 2023;67:30-5.
26. Meiser B, Quinn VF, Mitchell G, et al. Psychological outcomes and surgical decisions after genetic testing in women newly diagnosed with breast cancer with and without a family history. Eur J Hum Genet 2018;26:972-83.
27. Rosenberg SM, Dominici LS, Gelber S, et al. Association of Breast Cancer Surgery With Quality of Life and Psychosocial Well-being in Young Breast Cancer Survivors. JAMA Surg 2020;155:1035-42.
28. Kuijer A, Dominici LS, Rosenberg SM, et al. Arm Morbidity After Local Therapy for Young Breast Cancer Patients. Ann Surg Oncol 2021;28:6071-82.
29. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med 2017;377:1836-46.

Cite this article as: Cheah W, Kemp RS, Copson ER, Cutress RI. Biological features and locoregional recurrence in early-onset breast cancer: insights from the Young Women's Breast Cancer Study and the Prospective Study of Outcomes in Sporadic and Hereditary Breast Cancer. Gland Surg 2026;15(2):30. doi: 10.21037/gs-2025-1-578