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RESEARCH ARTICLE

Breast Cancer in Young Women: Analysis of Incidence, Clinicopathological Profile and Biological Behaviour in a Tertiary Care Institute from South India

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Abstract

Aims and Objectives: There is an increasing incidence of breast cancer in young women and many of these patients are considered to have more aggressive disease biology. The study aimed to find out the demographic profile, clinicopathological profile, and management details in patients under the age of 40 years treated for breast cancer in a tertiary care institute. **Materials and Methods:** The study retrospectively analysed all the females with biopsy proven breast cancer treated at our oncology department between January 2012 and December 2018. Patients aged below 40 years were stratified from the total breast cancer patients. The data related to demographic profile, clinical staging, pathological staging, hormonal status and treatment details were collected from medical records for the patients and analysed. **Results:** A total of 1056 biopsy proven breast cancer patients were treated during the study period. Out of which, the breast cancer patients under the age of 40 years were 161 (15.24%). The mean age at presentation was 33 years. Maximum patients were between the age group of 35 to 40 years (45.4%). Most of the patients were presented with Stage III (44%). Infiltrating Ductal Carcinoma, Grade II was the most common histologic type and grade. ER (Oestrogen Receptor) positivity seen in 49% of patients and PR (Progesterone receptor) Positivity in 49.7% and 46% had HeR2 Positivity. **Conclusion:** Our study concludes that the incidence of breast cancer patients under the age of 40 years is increasing. These patients tend to have higher grade tumours, Her2 Positive and triple-negative breast cancer. Young patients presenting with breast lumps should undergo all standard screening and diagnostic investigations must be carried out for early diagnosis and proper interventions.

Keywords: Breast cancer- young women- Prognostic factors- oestrogen receptor- progesterone receptor- HeR2

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Introduction

Breast cancer is the most common cancer affecting women globally, accounting for 25.4% of all new cancer cases. It is the leading cause of cancer death in 103 countries including India [1]. Recent years has noted a trend of increasing incidence of young breast cancer in India and it accounts for 10-20 % of all breast cancers [2-4]. Breast cancer in young females is unique in that it serves as a poor prognostic factor due to the greater incidence of advanced stage at presentation itself a poor prognosis factor because of greater incidence of advanced stage of disease at presentation [4]. The breast cancer in young Indian women appears to be associated with aggressive histology, loss of Oestrogen and Progesterone Receptor expression, with higher propensity for relapse, distant metastasis and higher mortality [5-9].Young age at diagnosis of breast cancer has emerged world-wide as an independent factor associated with higher risk of relapse and death in several large studies, even when more aggressive therapies are administered [10-14].

The diagnosis in young females is usually delayed because of low index of suspicion, firm breasts hindering clinical and radiological interpretation also causing

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missing of small breast lumps. Additionally, primary care doctors may also be reluctant to advice mammography in young patients because of the involved radiation. Relatively late detection and more aggressive nature of breast carcinoma is responsible for poor outcomes in these patients [15]. Expression of key biomarkers, including endocrine receptors, HER2 and proliferation markers, appears to be different in younger patients. Recent studies have attempted to control for tumour molecular subtypes, recognizing that more aggressive subtypes are more common in younger women. Two studies suggested particularly worse outcomes in young patients compared to older women with luminal-B tumours [12, 14].

Despite the data available in the specialist literature, it is not yet clear whether breast cancers arising in young women are biologically different from those found in older women. Most of the published studies on this issue have focused on relatively large cohorts of premenopausal patients.[16-18] This was a hospital based retrospective observational study conducted to study various aspects of breast cancer occurring in patients younger than 40 years of age. Our emphasis was in analysing tumour characteristics among younger patients with breast cancer.

Materials and Methods

This was a hospital based retrospective observational study conducted at our oncology department between 2012 to 2018. Retrospective record-based analysis of all the breast cancer patients treated at our institute have been collected. Breast cancer patients under the age of 40 years were stratified from the total breast cancer population. Demographic, clinical, pathological and treatment details were collected from medical records.

Histopathology study was considered as a gold standard of diagnosis. Histopathological details and Immunohistochemistry (IHC) status (Oestrogen, Progesterone and Her2 receptors) were obtained from histopathology records. Cancer staging done as per TNM classification in American Joint Committee on Cancer Staging System. Histologic grading of breast carcinoma was performed using Nottingham Histologic Score. Treatment details including Surgery, Chemotherapy, Radiation Therapy and Hormonal Details were collected and retrospectively analysed.

Data was collected and tabulated into a master sheet and statistical tests were applied to test the significance of association. The results were studied using appropriate statistical methods. Descriptive analysis and inferential analysis have been done in the study. p value less than equal to 0.05 was taken as statistically significant. Microsoft word and excel were used for generating charts and graphs SPSS version 22 was used for statistical analysis.

Results

A total 161 patients of biopsy proven breast cancer who were below 40 years of age were included in study. The Patient and Tumour Characteristics are shown in Table 1. Mean age of 33 years (range: 25-40 years) was noted. Most Predominant age group was 35-40 years (45.4%) and 30-35 years (40.3%). Right breast was the most common site of occurrence.

The maximum number of patients presented with Clinical Stage III 71 patients (44%) followed by stage II which comprised of 68 patients. Metastasis was seen in eight cases in which the bones being the most common site of metastasis. Core needle biopsy was the main initial modality of diagnosis. Mammogram was undertaken by all the patients. Infiltrating Ductal Carcinoma most predominant histology and Grade II was the most common grade. With regards to hormonal status, ER positivity was seen in 49% of patients and PR Positivity in 49.7% and 46% had HeR2 Positivity. 51% were Triple Negative.

In Treatment, 60% of the patients underwent Neoadjuvant chemotherapy. Surgery was the standard of treatment in all the patients. 56% had undergone Modified Radical Mastectomy (MRM) and 39% Breast Conservation Surgery (BCS). Stage III was the predominant stage in the pathologically. A total of 146 patients were undergone adjuvant radiation as a part of Breast Conservation Therapy or with high-risk features in patients who underwent MRM. 60% had received External Beam Radiation Therapy (EBRT) with a radiation dose 50 Gray in 25 fractions either by 3DCRT (3D Conformal Radiotherapy) or IMRT (Intensity Modulated Radiotherapy). Adjuvant chemotherapy was taken by 40% and hormone treatment was undertaken by 47.7% patients and Treatment Details are given in Table 2.

Discussion

Breast cancer in females of age 40 years and younger, is a rare and it presents a serious concern in diagnosis and adequate management of the disease in developing

Table1. Patient and Tumour Characteristics

Variable		Number	Percentage	p Value
Site	Right Breast	95	59	0.04
	Left Breast	66	41	
Age	Less than 30	23	14.3	0.04
	30-35	65	40.3	
	35-40	73	45.4	
Stage	Stage 1	9	5.5	0.07
	Stage 2	68	42.2	
	Stage 3	71	44	
	Stage 4	13	8	
ER	Positive	79	49	0.05
	Negative	82	51	
PR	Positive	80	49.7	
	Negative	81	50.3	
HeR2	Positive	74	46	
	Negative	87	54	
	Triple Positive	74	46	0.2
	Triple Negative	82	51	

Table 2. Post Operative Staging and Treatment Details

Variable		Number	Percentage	p Value
Surgery	BCS	77	51	0.45
	MRM	76	49	
Post Operative Staging	Stage I	5	3	0.07
	Stage II	65	42.4	
	Stage III	70	45.7	
	Stage IV	13	8	
Chemotherapy	Neoadjuvant chemotherapy	92	60	
	Adjuvant chemotherapy	61	40	
Radiotherapy	3DCRT	92	63	
	IMRT	54	37	

countries [19, 20]. Our comprehensive study represents the cohort of Young Breast Cancer patients from India. Biological age can't be measured accurately and thus we used the ESO-ESMO guidelines age cut off as <40 years for YBC (Young Breast Cancer) to determine our study participants [21].

The incidence varies from 2 to 6% in west to 10–20% in Asia [22-25]. It was interesting to note that more than half of our study patients belonged to the 36–40 years age group. Yet, the scant literature reporting on Breast Cancer in young women is ironical. The incidence in India has been reported as per Surveillance, Epidemiology, and End Results (SEER) data analysis among Asian women 16.2% ($p < 0.0001$) [26]. In our study, the proportion of YBC was 15.24% which is similar to the SEER data and the other related studies [7, 27-30]. It is widely believed that breast cancer in young women is characterized by a relatively unfavourable prognosis and unusual pathological features. This was an observational study which was designed to find out the unique features of breast cancer in young female.

In our study most common presenting complaint was breast lump which was present in all the patients (100%). Breast lump was the commonest presentation of breast cancers across the various studies [31-33].

According to the SEER study, the mean age of diagnosis, was 34.8 years while in our study it was 33 years [34]. Left breast was the predominant site of occurrence 50.8%, in previous studies, [35] however in our study it was the right breast most commonly affected. Histologically, the predominance of infiltrating ductal carcinoma case reported in our study is corroborated in numerous reports in the literature databases [36,37]. Women younger than 35 have a lower rate of ductal carcinoma in situ, which was the similar observation in our study [38].

In our study Grade 2 was most common histologic grade, which is similar to the studies conducted by Papalexis P. et al and Chollet-Hinton L [39,40]. Stage III was the most common disease stage in our population, which is similar to western studies that young women are more likely to be diagnosed at a more advanced stage [41]. Six percent (6%) of women have cancer that has spread outside of the breast at the time they are first diagnosed with breast cancer [42]. Similarly, our study had 5% of the breast cancer patients had distant metastasis at presentation.

Young women are more likely to develop breast cancer with more aggressive biological features compared to older women. These features include larger tumour size, advanced tumour stage, negative hormone receptors status (ER and PR), and overexpression of the human epidermal growth factor receptor 2 (HER2), [43,44] all contributing to the poorer prognosis among young female patients with breast cancer. We had 49% cases with ER PR positivity and 46 % cases with HER2 positivity. Hormone positivity of our study population is comparable with French cohort (41.5% vs 39.8%) but with a higher HER2 positivity (46% vs 38%) [45]. In line with previous literature our study also showed that patients <40 years more often have Breast Cancer with a Triple Negative and HER2 Positive subtype [46-48].

Both immunohistochemical (IHC) and molecular classifications have been employed to address whether cancer biology defines a unique disease in young women with breast cancer [49-52]. Evaluation of these four Luminal subtypes in a cohort of 2,970 young patients, which included a subset of young women with breast cancer, indicated that there were significantly more patients with triple-negative subtypes and significantly fewer luminal A subtypes in the young patient cohort when compared with the old women [12]. Other studies have also identified luminal subtypes in older patients [53], with triple-negative subtypes overrepresented in women younger than 40 years of age [54]. The finding that young patients with tumours classified as luminal B, HER-2 enriched and triple-negative subtypes were at increased risk of relapse when compared with older patients with the same subtype [55], suggests that younger patients with breast cancer may exhibit an aggressive biology.

The trend analyses show that young patients are increasingly treated with Neoadjuvant Systemic therapy followed by locoregional treatment which is according to earlier reports [56,35]. In our analyses the most pronounced increase in the use of neoadjuvant treatment was seen in young patients with TN and HER2 positive tumours. Previous studies described that young patients are more likely to undergo mastectomy [37,57]. In our

study mastectomy percentages in young patients was 56%.

In conclusion, the proportion of Breast cancer in young patients appears to be higher and represent a distinct subgroup. It is alarming to note that even in the current era, more than half of the patients present at an advanced stage, high grade, triple-negative and Her 2 positive subtypes which calls for cancer awareness and escalation of screening programmes. It has many clinical and biological features that must be considered during treatment. Finally, better characterization of somatic mutations in these tumours using next generation sequencing could further identify key driver mutations that can be targeted in this challenging disease.

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Competing interests

There was no conflict of interests

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians. 2021 05;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Varughese AA, Poothiode U, Manjula VD. Descriptive study on selected risk factors and histopathology of breast carcinoma in a tertiary care centre in Kerala, India with special reference to women under 40 years old. Asian Pacific journal of cancer prevention: APJCP. 2015;16(1):181-184. https://doi.org/10.7314/apjcp.2015.16.1.181
3. Gogia A, Raina V, Deo SVS, Shukla NK, Mohanti BK. Young breast cancer: A single center experience. Indian Journal of Cancer. 2014;51(4):604-608. https://doi.org/10.4103/0019-509X.175332
4. Tfayli A, Temraz S, Abou Mrad R, Shamseddine A. Breast cancer in low- and middle-income countries: an emerging and challenging epidemic. Journal of Oncology. 2010;2010:490631. https://doi.org/10.1155/2010/490631
5. Ghosh S, Sarkar S, Simhareddy S, Kotne S, Rao PBA, Turlapati SPV. Clinico-morphological profile and receptor status in breast cancer patients in a South Indian institution. Asian Pacific journal of cancer prevention: APJCP. 2014;15(18):7839-7842. https://doi.org/10.7314/apjcp.2014.15.18.7839
6. Martínez MT, Oltra SS, Peña-Chilet M, Alonso E, Hernando C, Burgues O, Chirivella I, Bermejo B, Lluch A, Ribas G. Breast Cancer in Very Young Patients in a Spanish Cohort: Age as an Independent Bad Prognostic Indicator. Breast Cancer: Basic and Clinical Research. 2019;13:1178223419828766. https://doi.org/10.1177/1178223419828766
7. Kothari AS, Beechey-Newman N, D'Arrigo C, Hanby AM, Ryder K, Hamed H, Fentiman IS. Breast carcinoma in women age 25 years or less. Cancer. 2002 02 01;94(3):606-614. https://doi.org/10.1002/cncr.10273
8. Takalkar1 UV, Asegaonkar SB, Kulkarni U, Saraf M, Advani S. Clinicopathological Profile of Breast Cancer Patients at a Tertiary Care Hospital in Marathwada Region of Westen India. Asian Pacific journal of cancer prevention: APJCP. 2016;17(4):2195-2198. https://doi.org/10.7314/apjcp.2016.17.4.2195
9. Parmar V. Rising Incidence of Breast Cancer in the Young Fertile Indian Population-a Reality Check. Indian Journal of Surgical Oncology. 2018 09;9(3):296-299. https://doi.org/10.1007/s13193-018-0800-4
10. Gnerlich JL, Deshpande AD, Jeffe DB, Sweet A, White N, Margenthaler JA. Elevated breast cancer mortality in women younger than age 40 years compared with older women is attributed to poorer survival in early-stage disease. Journal of the American College of Surgeons. 2009 03;208(3):341-347. https://doi.org/10.1016/j.jamcollsurg.2008.12.001
11. Fredholm H, Eaker S, Frisell J, Holmberg L, Fredriksson I, Lindman H. Breast cancer in young women: poor survival despite intensive treatment. PloS One. 2009 Nov 11;4(11):e7695. https://doi.org/10.1371/journal.pone.0007695
12. Cancello G, Maisonneuve P, Rotmensz N, Viale G, Mastropasqua MG, Pruneri G, et al. Prognosis and adjuvant treatment effects in selected breast cancer subtypes of very young women (<35 years) with operable breast cancer. Annals of Oncology. 2010 Oct 01;21(10):1974-1981. https://doi.org/10.1093/annonc/mdq072
13. Han W, Kang SY. Relationship between age at diagnosis and outcome of premenopausal breast cancer: age less than 35 years is a reasonable cut-off for defining young age-onset breast cancer. Breast Cancer Research and Treatment. 2010 01;119(1):193-200. https://doi.org/10.1007/s10549-009-0388-z
14. Azim HA, Michiels S, Bedard PL, Singhal SK, Criscitiello C, Ignatiadis M, Haibe-Kains B, Piccart MJ, Sotiriou C, Loi S. Elucidating prognosis and biology of breast cancer arising in young women using gene expression profiling. Clinical Cancer Research: An Official Journal of the American Association for Cancer Research. 2012 03 01;18(5):1341-1351. https://doi.org/10.1158/1078-0432.CCR-11-2599
15. Anders CK, Fan C, Parker JS, Carey LA, Blackwell KL, Klauber-DeMore N, Perou CM. Breast carcinomas arising at a young age: unique biology or a surrogate for aggressive intrinsic subtypes?. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 2011 01 01;29(1):e18-20. https://doi.org/10.1200/JCO.2010.28.9199
16. Macêdo Andrade AC, Ferreira Júnior CA, Dantas Guimarães B, Pessoa Barros AW, Sarmento de Almeida G, Weller M. Molecular breast cancer subtypes and therapies in a public hospital of northeastern Brazil. BMC women's health. 2014 09 12;14:110. https://doi.org/10.1186/1472-6874-14-110
17. Walker RA, Lees E, Webb MB, Dearing SJ. Breast carcinomas occurring in young women (< 35 years) are different. British Journal of Cancer. 1996 Dec;74(11):1796-1800. https://doi.org/10.1038/bjc.1996.632
18. Villarreal-Garza C, Platas A, Miaja M, Fonseca A, Mesa-Chavez F, Garcia-Garcia M, Chapman J, et al. Young Women With Breast Cancer in Mexico: Results of the Pilot Phase of the Joven & Fuerte Prospective Cohort. JCO global oncology. 2020 03;6:395-406. https://doi.org/10.1200/JGO.19.00264
19. Paluch-Shimon S, Cardoso F, Partridge AH, Abulkhair O, Azim HA, Bianchi-Micheli G, Cardoso M, et al. ESO-ESMO 4th International Consensus Guidelines for Breast

Cancer in Young Women (BCY4). Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2020 06;31(6):674-696. https://doi.org/10.1016/j.annonc.2020.03.284
20. Ryu JM, Yu J, Kim SI, Kim KS, Moon H, Choi JE, et al. Different prognosis of young breast cancer patients in their 20s and 30s depending on subtype: a nationwide study from the Korean Breast Cancer Society. Breast Cancer Research and Treatment. 2017 Dec;166(3):833-842. https://doi.org/10.1007/s10549-017-4472-5
21. Nair N, Shet T, Parmar V, Havaldar R, Gupta S, Budrukkar A, Sarin R, et al. Breast cancer in a tertiary cancer center in India - An audit, with outcome analysis. Indian Journal of Cancer. 2018;55(1):16-22. https://doi.org/10.4103/ijc.IJC_484_17
22. Bhan N, Madhira P, Muralidharan A, Kulkarni B, Murthy G, Basu S, Kinra S. Health needs, access to healthcare, and perceptions of ageing in an urbanizing community in India: a qualitative study. BMC geriatrics. 2017 07 19;17(1):156. https://doi.org/10.1186/s12877-017-0544-y
23. Dey S, Nambiar D, Lakshmi JK, Sheikh K, Reddy KS. Health of the elderly in India: challenges of access and affordability. InAging in Asia: Findings from new and emerging data initiatives 2012. National Academies Press (US).
24. Deshmukh SP, Mane AD, Zade BP , Sane SP. Breast Cancer in Young Women in India. Annals of Oncology, ISSN: 0923-7534, Vol: 23, Page: ix101.2012.
25. Bertheau P, Steinberg SM, Cowan K, Merino MJ. Breast cancer in young women: clinicopathologic correlation. Seminars in Diagnostic Pathology. 1999 08;16(3):248-256.
26. Colleoni M, Rotmensz N, Robertson C, Orlando L, Viale G, Renne G, Luini A, et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. Annals of Oncology: Official Journal of the European Society for Medical Oncology. 2002 02;13(2):273-279. https://doi.org/10.1093/annonc/mdf039
27. Giaquinto AN, Sung H, Miller KD, Kramer JL, Newman LA, Minihan A, Jemal A, Siegel RL. Breast Cancer Statistics, 2022. CA: a cancer journal for clinicians. 2022 Nov;72(6):524-541. https://doi.org/10.3322/caac.21754
28. Cathcart-Rake EJ, Ruddy KJ, Bleyer A, Johnson RH. Breast Cancer in Adolescent and Young Adult Women Under the Age of 40 Years. JCO oncology practice. 2021 06;17(6):305-313. https://doi.org/10.1200/OP.20.00793
29. Ellington TD, Miller JW, Henley SJ, Wilson RJ, Wu M, Richardson LC. Trends in Breast Cancer Incidence, by Race, Ethnicity, and Age Among Women Aged ≥20 Years - United States, 1999-2018. MMWR. Morbidity and mortality weekly report. 2022 01 14;71(2):43-47. https://doi.org/10.15585/mmwr.mm7102a2
30. Bloom HJG. Further studies on prognosis of breast carcinoma. British Journal of Cancer. 1950 Dec;4(4):347-367. https://doi.org/10.1038/bjc.1950.34
31. Noyes RD, Spanos WJ, Montague ED. Breast cancer in women aged 30 and under. Cancer. 1982 03 15;49(6):1302-1307. https://doi.org/10.1002/1097-0142(19820315)49:6<1302::aid-cncr2820490638>3.0.co;2-0
32. Pollán M, Pastor-Barriuso R, Ardanaz E, Argüelles M, Martos C, Galcerán J, Sánchez-Pérez M, et al. Recent changes in breast cancer incidence in Spain, 1980-2004. Journal of the National Cancer Institute. 2009 Nov 18;101(22):1584-1591. https://doi.org/10.1093/jnci/djp358
33. Darré T, Tchaou M, Folligan K, Amadou A, N'Timon B, Sonhaye L, Aboubakari A, Amégbor K, Akpadza K, Napo Koura G. Breast cancer cases of female patients under 35 years of age in Togo: A series of 158 cases. Molecular and Clinical Oncology. 2017 Dec;7(6):1125-1129. https://doi.org/10.3892/mco.2017.1461
34. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. CA: a cancer journal for clinicians. 2000;50(1):7-33. https://doi.org/10.3322/canjclin.50.1.7
35. Gueye M, Kane Gueye SM, Ndiaye Gueye MD, Niasse Dia F, Gassama O, Diallo M, Moreau JC. Breast cancer in women younger than 35 years : features and outcomes in the breast unit at Aristide le Dantec Teaching Hospital, Dakar. Medecine Et Sante Tropicales. 2016 Nov 01;26(4):377-381. https://doi.org/10.1684/mst.2016.0637
36. Winchester DP, Osteen RT, Menck HR. The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age. Cancer. 1996 Oct 15;78(8):1838-1843. https://doi.org/10.1002/(sici)1097-0142(19961015)78:8<1838::aid-cncr27>3.0.co;2-y
37. Erić I, Petek Erić A, Kristek J, Koprivčić I, Babić M. Breast cancer in young women: Pathologic and immunohistochemical features. Acta Clinica Croatica. 2018 09;57(3):497-502. https://doi.org/10.20471/acc.2018.57.03.13
38. Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, Abner A, Recht A, Vicini F, Harris JR. Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology. 1994 05;12(5):888-894. https://doi.org/10.1200/JCO.1994.12.5.888
39. Papalexis P, Georgakopoulou VE, Keramydas D, Vogiatzis R, Taskou C, Anagnostopoulou FA, Nonni A, et al. Clinical, Histopathological, and Immunohistochemical Characteristics of Predictive Biomarkers of Breast Cancer: A Retrospective Study. Cancer Diagnosis & Prognosis. 2024;4(3):340-351. https://doi.org/10.21873/cdp.10330
40. Chollet-Hinton L, Anders CK, Tse C, Bell MB, Yang YC, Carey LA, Olshan AF, Troester MA. Breast cancer biologic and etiologic heterogeneity by young age and menopausal status in the Carolina Breast Cancer Study: a case-control study. Breast cancer research: BCR. 2016 08 04;18(1):79. https://doi.org/10.1186/s13058-016-0736-y
41. Warner ET, Colditz GA, Palmer JR, Partridge AH, Rosner BA, Tamimi RM. Reproductive factors and risk of premenopausal breast cancer by age at diagnosis: are there differences before and after age 40?. Breast Cancer Research and Treatment. 2013 Nov;142(1):165-175. https://doi.org/10.1007/s10549-013-2721-9
42. Vaz-Luis I, Cottu P, Mesleard C, Martin AL, Dumas A, Dauchy S, Tredan O, et al. UNICANCER: French prospective cohort study of treatment-related chronic toxicity in women with localised breast cancer (CANTO). ESMO open. 2019;4(5):e000562. https://doi.org/10.1136/esmoopen-2019-000562
43. Murphy BL, Day CN, Hoskin TL, Habermann EB, Boughey JC. Adolescents and Young Adults with Breast Cancer have More Aggressive Disease and Treatment Than Patients in Their Forties. Annals of Surgical Oncology. 2019 Nov;26(12):3920-3930. https://doi.org/10.1245/s10434-019-07653-9
44. Keegan THM, DeRouen MC, Press DJ, Kurian AW, Clarke CA. Occurrence of breast cancer subtypes in adolescent and young adult women. Breast cancer research: BCR. 2012 03 27;14(2):R55. https://doi.org/10.1186/bcr3156
45. Wang K, Ren Y, Li H, Zheng K, Jiang J, Zou T, Ma B, et al. Comparison of Clinicopathological Features and Treatments between Young (≤40 Years) and Older (>40 Years) Female Breast Cancer Patients in West China: A Retrospective,

Epidemiological, Multicenter, Case Only Study. PloS One. 2016;11(3):e0152312. https://doi.org/10.1371/journal.pone.0152312
46. Shoemaker ML, White MC, Wu M, Weir HK, Romieu I. Differences in breast cancer incidence among young women aged 20-49 years by stage and tumor characteristics, age, race, and ethnicity, 2004-2013. Breast Cancer Research and Treatment. 2018 06;169(3):595-606. https://doi.org/10.1007/s10549-018-4699-9
47. Landercasper J, Bennie B, Parsons BM, Dietrich LL, Greenberg CC, Wilke LG, Linebarger JH. Fewer Reoperations After Lumpectomy for Breast Cancer with Neoadjuvant Rather than Adjuvant Chemotherapy: A Report from the National Cancer Database. Annals of Surgical Oncology. 2017 06;24(6):1507-1515. https://doi.org/10.1245/s10434-016-5760-8
48. Mougalian SS, Soulos PR, Killelea BK, Lannin DR, Abu-Khalaf MM, DiGiovanna MP, Sanft TB, Pusztai L, Gross CP, Chagpar AB. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. Cancer. 2015 08 01;121(15):2544-2552. https://doi.org/10.1002/cncr.29348
49. Kim E, Noh WC, Han W, Noh D. Prognostic significance of young age (<35 years) by subtype based on ER, PR, and HER2 status in breast cancer: a nationwide registry-based study. World Journal of Surgery. 2011 06;35(6):1244-1253. https://doi.org/10.1007/s00268-011-1071-1
50. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, Deng S, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proceedings of the National Academy of Sciences of the United States of America. 2003 07 08;100(14):8418-8423. https://doi.org/10.1073/pnas.0932692100
51. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, Hastie T, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proceedings of the National Academy of Sciences of the United States of America. 2001 09 11;98(19):10869-10874. https://doi.org/10.1073/pnas.191367098
52. Perou CM, Sørlie T, Eisen MB, Rijn M, Jeffrey SS, Rees CA, Pollack JR, et al. Molecular portraits of human breast tumours. Nature. 2000 08 17;406(6797):747-752. https://doi.org/10.1038/35021093
53. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, Karaca G, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA. 2006 06 07;295(21):2492-2502. https://doi.org/10.1001/jama.295.21.2492
54. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 05 01;109(9):1721-1728. https://doi.org/10.1002/cncr.22618
55. Clough KB, Acosta-Marín V, Nos C, Alran S, Rouanet P, Garbay J, Giard S, et al. Rates of Neoadjuvant Chemotherapy and Oncoplastic Surgery for Breast Cancer Surgery: A French National Survey. Annals of Surgical Oncology. 2015 Oct;22(11):3504-3511. https://doi.org/10.1245/s10434-015-4378-6
56. Spronk PER, Volders JH, Tol P, Smorenburg CH, Vrancken Peeters MTFD. Breast conserving therapy after neoadjuvant chemotherapy; data from the Dutch Breast Cancer Audit. European Journal of Surgical Oncology: The Journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2019 02;45(2):110-117. https://doi.org/10.1016/j.ejso.2018.09.027
57. Bleyer A, O'Leary M, Barr R, Ries L, Bethesda MD. Cancer epidemiology in older adolescents and young adults 15 to 29 years of age, including SEER incidence and survival: 1975-2000. National Cancer Inst. 2006.