

REVIEW ARTICLE

Review of Breast Cancer in Young Women

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ABSTRACT

Abnormal malignant growth of breast cells often occurs among women after menopause. But, recently, breast cancer (BC) is increasing in trend among young women, mainly in Asian countries. Breast cancer in young women (BCYW) usually presented with higher grades, advanced stage, and aggressive subtype. The survival of BCYW is poor with a more progressive and higher chance of recurrence and metastasis. Treatment for BCYW usually is more intensive and extensive, which causes more side effects that potentially lead to psychosocial issues. This article review highlights the unique and complex issues of BCYW in Malaysia and around the world.

Keywords: Breast Cancer, Young women, Premenopause, Prognosis, Survival

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INTRODUCTION

Breast cancer have been the utmost disease in women for decades. According to GLOBOCAN, in 2018, two million women were diagnosed with breast cancer, which equivalent to 32.7% of all cancer among women. In recent times, breast cancer has become more frequent among young women (1). In America, approximately seven per cent of breast cancer patients are young women of 40 years and less (2,3). The American Cancer Society also estimated that 12,150 breast cancer cases in 2017 were women age less than 40, and 26,393 were women under the age of 45 (4).

A similar trend also seen in Asian countries but with a harder situation, where most of the breast cancer patients age between 40 and 50 years in comparison with 60 to 70 years in the Western population (5–7). Indonesian women often diagnosed much younger, approximately 37 years (8) comparing with other Asian countries (9,10). The incidence rate of breast cancer in young women (BCYW) age 40 years and below in South East Asia population were 11.4% in Indonesia (8), 13.6% in Malaysia (11), 16.2% in India (12), 19.1% in Singapore (13), 26% in Northern India (14), and 27.9% in Nepal (15). A data compiled from breast cancer registration in hospitals from Malaysia and Singapore have reported

that 15% of breast cancer women were diagnosed at the age of less than 40 years (16). These figures show that the incidence of BCYM in Asia is high and increasing, in comparison to 6.2% among Caucasians in America (4). For ethnicity, Malays had a significantly younger mean age at diagnosis which is 46 years than Indian and Chinese in Malaysia (17).

The World Health Organization (WHO) had estimated 627,000 breast cancer deaths in the year 2018, equivalent to 15% of all cancer deaths among women worldwide (1). Despite high breast cancer incidence rates in developed countries where mostly diagnosed at a later age, the survival rate and prognosis are better than in developing countries (5). Malaysia ranked the second-highest cancer mortality rate in South-Eastern Asia countries, accounting for 18.4 per 100,000 populations after 18.5 in Singapore (1). Breast cancer were the first leading cause of all cancer death for women in Malaysia (1) with 5-year overall survival of 43.5% to 75.7%, and 68 months of median survival time (6,10,19,20) with Malays ethnicity is significantly associated with poorer survival (17). International comparisons with selected Asian countries showed that breast cancer survival in Malaysia was higher than in India and Thailand but lower than Singapore, China, Korea, and Japan (21).

There are many risk factors contributing to breast cancer in young women (BCYW). One of the factors is the unhealthy lifestyle among the younger generation of women. Unhealthy lifestyle habits such as eating high fat foods, being physically inactive and being obese

are at high risk for breast cancer, as well as smoking, not having children, not breastfeeding, birth control, hormonal therapy and breast implant (22).

PROGNOSTIC FACTORS

Age of patient during diagnosis of the disease is frequently associated with the prognosis of a breast cancer patient (23,24). Most studies suggested significantly poorer clinical outcomes among BCYW (25,26). Previous cohort study (27) revealed that young women were 40% poorer survival than 40 years and above. Another study (23) found that breast cancer survival worsens among women below 35 years (69%) and 35-39 years (76%) as compared to age 40-49 years (84%) and age 50-69 years (89%) respectively. Besides, young women were also found to have a shorter time of recurrence, which further increased the likelihood of dying from this disease (26). These may support that young age at diagnosis is contributing to lower survival (27-31).

Ethnicity is another significant predictor of breast cancer survivorship. A study on Asian American subgroups (32) found that Hispanic-American (69.4%) had the lowest survival compared to Hawaiian (74.6%), Hispanic white (77%), non-Hispanic whites (80%), Filipino (81.1%), Asian Indian/Pakistani (82.5%), Asian (83.5%), Chinese (84.8%), Japanese (86%), Vietnamese (86.1%), Korean (88.3%) and Others (89.5%). Meanwhile, studies conducted in Malaysia and Singapore (10,11,16,17) found that Malays had lower survival in comparison to Indian and Chinese. Nevertheless, when comparing between two countries, Malaysian Malay, Chinese and Indian had a much lower 5-year survival rate of 39.7%, 48.2%, and 47.2%, respectively, compared to the 54.1%, 73.1%, and 65.2% respectively, in Singapore (16,17). Although higher incidence rates were presented by Chinese ethnic in Malaysia with ASR 40.7 per 100,000 compared to Malay with ASR 28.0 per 100,000 populations (33), the projection was worst among Malays (6,10,11,19). Malay often found to be diagnosed at later stages (34-36) may explain to its poor survival. Besides, poor health-seeking behaviour, non-adherence to treatment, and practice of alternative and complementary medicine might be the reasons for poor prognosis among Malay (10,20,37,38). However, studies concentrating on ethnic disparities in survivorship of young breast cancer women remain scarce in Malaysia.

Stage of disease significantly predicts survivorship in BCYW, where the survival reduced with increases in disease stage (32,39-41). Previous studies reported a significantly longer median survival time for stage I and II breast cancer (42 to 164 months) in comparison to stage III and IV (6.9 to 53 months) regardless of age at diagnosis (8,10,16,40). Besides that, young breast cancer women often found with a later stage and higher grades (42-45). A retrospective study (42) reported

that younger women had a 60% higher chance to be diagnosed at later-stage as compared to 36 years and older. However, younger women with late-stage disease survive better compared to older women with the same disease stage (2).

Types of breast cancer affect the survivorship of young women. Breast cancer is classified into four main types, includes metastatic BC, inflammatory BC, invasive ductal carcinoma, and ductal carcinoma in situ (46). Eighty per cent of BC were invasive ductal carcinoma, and it is found more aggressive in young women below 35 years (47), indicating a worse prognosis (3). Triple-negative breast cancer (TNBC), an intrinsic subtype, occurs in 10 to 20% of breast cancer cases (48), often affect younger women and those with a BRCA1 gene mutation (47,49-51). A study in Korea (52) comparing TNBC found that younger patients (74.8%) had lower survival than those more than 35 years (83.9%).

Moreover, different molecular subgroups include basal-like, normal-like, luminal A, luminal B, and HER2-positive (53), also found contributing to the survivorship of breast cancer. Previous studies revealed that luminal A (23,54,55), luminal B (54,55), and estrogen receptor-negative tumours (52,56) show higher mortality risk among young women below 35 years, but in HER-2 subtypes, the finding was contradicted (3,44,47). Stromal-related gene signatures are other significant prognostic factors found predicting survivorship in younger breast cancer women, suggesting the behaviour of tumour cells is affected by the microenvironment (3,57,58). A gene expression analysis study reported a worsening prognosis by the C1Q gene, while HLA genes improve survival (59). Another cohort study also revealed that increased stroma gene expression predicts the chemotherapy resistance in estrogen receptor-negative breast cancer thus affect the prognosis (60).

GENETIC AND HEREDITARY FACTORS

Genetic and hereditary factors may be the primary factors that lead to breast cancer, particularly among younger women (61). Women with closed relatives having breast cancer were more likely to have the same disease (62). Mutation of the BRCA gene, which occurs in 0.25% of the population, increase the risk of breast cancer at an earlier life. Germline mutation of BRCA1 and BRCA2 had been reported approximately five and three per cent, respectively, among the BCYW (15,63-65) comparing to 0.3% among the older patients (15). A meta-analysis study (66) also shows that 49 to 72% of young women who inherited BRCA1 mutations and 57 to 69% who inherited BRCA2 mutations are at a higher chance of developing the disease. BRCA1 and BRCA2 carrier had an exponential risk to develop breast cancer before 40 years and 50 years, respectively. Breast cancer patients with BRCA mutations were often younger and

triple-negative (67).

BRCA mutations and their effects on survival were found heterogeneous from various studies. A systematic review and meta-analysis study shows no effect of BRCA mutations on breast cancer survival (68). In contrast, a meta-analysis study suggested that BRCA mutations were associated with worsened survival (69), whereas another study suggests an indecisive conclusion (70). Therefore, the mutated BRCA gene might implicate earlier development of breast cancer among young women, but the effect of survivorship remains unclear.

SCREENING, TREATMENT, AND ADHERENCE

Currently, the standard screening methods for breast cancer include mammograms, clinical breast examination, and breast self-examination (71). Mammogram screening is usually conducted opportunistically, particularly in developing countries, as opposed to population-based screening (72). Practically, women aged 50 and above or 45 and above with high-risk category will be examined, thus invited to undergo mammogram screening. In Malaysia, a subsidized screening program is provided publicly but need to fulfil specific eligibility criteria (71). Alternatively, a young woman may undergo mammogram screening in private facilities but must bear the full cost of the investigation. Besides, the sensitivity of mammographic screening was also affected by the higher breast density in young women (73), especially in Asia, making it difficult to diagnose. As a result, women aged 45 and younger were less likely to be screened and prone to present late due to limited access and other factors. Monthly breast self-examination should be encouraged among the young woman to encounter this limitation (74). Adequate knowledge, positive attitude, and good practice about breast self-examination should be given to young women to promote early detection of breast cancer.

The main treatment option for breast cancer is surgery comprise of mastectomy (MAC) and breast-conserving surgery (BCS). Adjuvant therapy and neoadjuvant therapy include chemotherapy, radiotherapy, hormone therapy, and targeted therapy (75). Treatment types were found significant to prognosticate the outcome of breast cancer survival. The international guideline suggested that treatment decisions mainly depend on tumour biological characteristics and patients' comorbidities and preferences (76). Younger patients usually have lesser comorbidities and treatment toxicities, but this cannot be the reason for more aggressive treatment (77). A combination of adjuvant radiotherapy and BCS was the preferred choice for young women, which had reported a significant improved 10-year overall survival compared to MAC (78). Nevertheless, other study findings show no effect on young women undergoing MAC or BCS surgery and the risk of death (79) as the outcome was equivalent (75). However, it was an exception for metastatic cases

where MAC was found to reduced 28% risk of death (16,80).

Still, from a population-based analysis, it is shown that there are higher rates of MAC in younger women compared to their older counterparts (81). Large tumour size, aggressive phenotype, and genetic and hereditary factors were the leading cause of MAC (82). Meanwhile, BCS often found to have higher local-recurrence interval (LRI) at 5 and 10 years and lower distant-metastases and deaths (82). Concerns over the recurrence of cancer, the complication of radiotherapy, and prolonged surveillance might be the contributing factors for MAC among BCYW (75).

Chemotherapy is commonly used as adjuvant therapy to remove remaining malignant cells after surgery. Adjuvant chemotherapy significantly enhanced survival (75) and preferable in the young group (44,47). For metastatic breast cancers, chemotherapy is the primary treatment, whereas, for locally advanced tumours, neoadjuvant chemotherapy effectively shrinks the large tumours before surgery (75). Adjuvant radiotherapy is important in management of young breast cancer, it significantly reduced recurrence and improved survival (83,84). In aggressive subtype BC, whole breast irradiation were preferred as it effectively removed remaining malignant cell after surgery (84).

Endocrine treatment is particularly crucial among premenopausal women due to the negative prognostic value for women of young age (76). Although the optimum treatment value remains unclear, many selected young women respond well with hormone therapy only (85). The current study reported that long-termed tamoxifen used among BCYW had demonstrated better outcomes (85). Also, hormonal therapy shows improved survival in patients who had a BRCA1 mutation (69). However, the implications of long-term toxicity, which include premature menopause, and infertility, might need to be considered before treatment (47).

Long-termed adjuvant therapy required breast cancer patients to adhere to treatment, thus preventing recurrence of the disease (86). A previous study reported that approximately 35% nonadherent rate for oral chemotherapy (87). Intolerable side effects and reduction of functionality were the common reason for nonadherence (87). Young age is also related to the low adjuvant hormonal therapy adherence, which leads to higher mortality (44,88). Studies also reported 20-40% of the young patients (below 40 years) more likely to stopped hormonal therapies prematurely due to related adverse effects (89-93). Therefore, awareness of treatment toxicities should be encouraged to improve adherence, especially in long-term endocrine therapy, to demonstrate the efficacy and prevent recurrence and death due to early discontinuation of endocrine therapy (94).

CONCLUSION

Difficulty in diagnosing is the current challenge for the management of BCYW with high breast density. The intensive and extensive investigation for young women might take more extended diagnosis and treatment periods and the possible higher risk for recurrence and metastasis. These factors lead to a social impact that comprises high financial burden as well as psychological challenges, including sexuality, infertility from premature ovarian failure, body image, low self-esteem, unemployment, and supportive care needs. Breast cancer not only affects the personal health of an individual but also portrays an enormous impact on family health, society, productivity, and economic growth of the country. Therefore, multi-disciplinary management is essential to optimize clinical outcomes, especially for young women.

BCYW can be related to the cohort effect of late marriage, not breastfeeding, no children, working women, and economic distress. Although the number of BCYW is small, 11% worldwide (1), and 7 to 14% in Malaysia (10,11), it is progressively increasing over the years. Therefore, it is crucial to create awareness and inculcate the importance of early detection and treatment for all women, especially at a younger age. In many cases, early diagnosis, together with prompt management is the key to better survival.

ACKNOWLEDGEMENT

This study was funded by the Universiti Sains Malaysia Short-term grant (304/CIPPT/6315266).

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* [Internet]. 2018 Nov;68(6):394–424. Available from: <https://onlinelibrary.wiley.com/doi/abs/10.3322/caac.21492>
2. Brinton LA, Sherman ME, Carreon JD, Anderson WF. Recent Trends in Breast Cancer Among Younger Women in the United States. *JNCI J Natl Cancer Inst* [Internet]. 2008 Nov 19;100(22):1643–8. Available from: <https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/djn344>
3. Tichy JR, Lim E, Anders CK. Breast Cancer in Adolescents and Young Adults: A Review With a Focus on Biology. *J Natl Compr Cancer Netw* [Internet]. 2013 Sep 1;11(9):1060–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24029122>
4. DeSantis CE, Ma J, Goding Sauer A, Newman LA, Jemal A. Breast cancer statistics, 2017, racial disparity in mortality by state. *CA Cancer J Clin* [Internet]. 2017 Nov;67(6):439–48. Available from: <http://doi.wiley.com/10.3322/caac.21412>
5. Leong SPL, Shen Z-Z, Liu T-J, Agarwal G, Tajima T, Paik N-S, et al. Is Breast Cancer the Same Disease in Asian and Western Countries? *World J Surg* [Internet]. 2010 Oct 7;34(10):2308–24. Available from: <http://link.springer.com/10.1007/s00268-010-0683-1>
6. Abdullah NA, Mahiyuddin WRW, Muhammad NA, Ali ZM, Ibrahim L, Tamim NSI, et al. Survival Rate of Breast Cancer Patients In Malaysia: A Population-based Study. *Asian Pacific J Cancer Prev* [Internet]. 2013 Aug 30;14(8):4591–4. Available from: <http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2013&vnc=v14n8&sp=4591>
7. Chen C, Sun S, Yuan J-P, Wang Y-H, Cao T-Z, Zheng H-M, et al. Characteristics of breast cancer in Central China, literature review and comparison with USA. *The Breast* [Internet]. 2016 Dec;30:208–13. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977616000096>
8. Anwar SL, Raharjo CA, Herviastuti R, Dwianingsih EK, Setyoheriyanto D, Avanti WS, et al. Pathological profiles and clinical management challenges of breast cancer emerging in young women in Indonesia: a hospital-based study. *BMC Womens Health* [Internet]. 2019 Dec 6;19(1):28. Available from: <https://bmcwomenshealth.biomedcentral.com/articles/10.1186/s12905-019-0724-3>
9. Abdullah MM, Mohamed AK, Foo YC, Lee CML, Chua CT, Wu CH, et al. Breast Cancer Survival at a Leading Cancer Centre in Malaysia. *Asian Pacific J Cancer Prev* [Internet]. 2016 Jan 11;16(18):8513–7. Available from: <http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2016&vnc=v16n18&sp=8513>
10. Nordin N, Yaacob NM, Abdullah NH, Hairon SM. Survival time and prognostic factors for breast cancer among women in North-East Peninsular Malaysia. *Asian Pacific J Cancer Prev* [Internet]. 2018; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5980940/>
11. Ibrahim NI, Dahlui M, Aina EN, Al-Sadat N. Who are the Breast Cancer Survivors in Malaysia? *Asian Pacific J Cancer Prev* [Internet]. 2012 May 30;13(5):2213–8. Available from: <http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2012&vnc=v13n5&sp=2213>
12. Kakarala M, Rozek L, Cote M, Liyanage S, Brenner DE. Breast cancer histology and receptor status characterization in Asian Indian and Pakistani women in the U.S. - a SEER analysis. *BMC Cancer* [Internet]. 2010 Dec 11;10(1):191. Available from: <http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-10-191>
13. NRDO. Singapore Cancer Registry Annual Registry Report 2015. *Cancer Reports*. 2017.
14. Nandakumar A, Gupta PC, Gangadharan P, Visweswara RN, Parkin DM. Geographic

- pathology revisited: Development of an atlas of cancer in India. *Int J Cancer* [Internet]. 2005 Sep 20;116(5):740–54. Available from: <http://doi.wiley.com/10.1002/ijc.21109>
15. Thapa B, Singh Y, Sayami P, Shrestha UK, Sapkota R, Sayami G. Breast Cancer in Young Women from a Low Risk Population in Nepal. *Asian Pacific J Cancer Prev* [Internet]. 2013 Sep 30;14(9):5095–9. Available from: <http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2013&vnc=v14n9&sp=5095>
 16. Bhoo Pathy N, Yip CH, Taib NA, Hartman M, Saxena N, lau P, et al. Breast cancer in a multi-ethnic Asian setting: Results from the Singapore–Malaysia hospital-based breast cancer registry. *The Breast* [Internet]. 2011 Apr;20:S75–80. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977611000324>
 17. Bhoo-Pathy N, Hartman M, Yip C-H, Saxena N, Taib NA, Lim S-E, et al. Ethnic Differences in Survival after Breast Cancer in South East Asia. Aziz SA, editor. *PLoS One* [Internet]. 2012 Feb 21;7(2):e30995. Available from: <http://dx.plos.org/10.1371/journal.pone.0030995>
 18. Ferlay J, Colombet M and Bray F. Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon, France: International Agency for Research on Cancer; 2018. Available from: <http://ci5.iarc.fr>
 19. Taib NA, Akmal MN, Mohamed I, Yip CH. Improvement in survival of breast cancer patients - Trends in survival over two time periods in a single institution in an Asia Pacific country, Malaysia. *Asian Pacific J Cancer Prev* [Internet]. 2011; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/21545192>
 20. Taib NA, Yip CH, Ibrahim M, Ng CJ, Farizah H. Breast cancer in malaysia: are our women getting the right message? 10 year-experience in a single institution in Malaysia. *Asian Pac J Cancer Prev* [Internet]. 2007;8(1):141–5. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17477791>
 21. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. *Lancet* [Internet]. 2018 Mar 17;391(10125):1023–75. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/29395269>
 22. Kudela E, Samec M, Kubatka P, Nachajova M, Laucekova Z, Liskova A, et al. Breast cancer in young women: Status quo and advanced disease management by a predictive, preventive, and personalized approach. *Cancers (Basel)*. 2019;11(11):1–20.
 23. Fredholm H, Magnusson K, Lindstrum LS, Garmo H, Fält SE, Lindman H, et al. Long-term outcome in young women with breast cancer: a population-based study. *Breast Cancer Res Treat* [Internet]. 2016 Nov 13;160(1):131–43. Available from: <http://link.springer.com/10.1007/s10549-016-3983-9>
 24. Owrang M, Copeland Jr RL, Ricks-Santi LJ, Gaskins M, Beyene D, Dewitty Jr RL, et al. Breast Cancer Prognosis for Young Patients. In Vivo [Internet]. 2017 Jul 3;31(4):661–8. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/28652435>
 25. Brenner DR, Brockton NT, Kotsopoulos J, Cotterchio M, Boucher BA, Courneya KS, et al. Breast cancer survival among young women: a review of the role of modifiable lifestyle factors. *Cancer Causes Control* [Internet]. 2016/03/12. 2016 Apr 12;27(4):459–72. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/26970739>
 26. Marthnez MT, Oltra SS, Peca-Chilet M, Alonso E, Hernando C, Burgues O, et al. Breast Cancer in Very Young Patients in a Spanish Cohort: Age as an Independent Bad Prognostic Indicator. *Breast Cancer Basic Clin Res* [Internet]. 2019 Jan 20;13:117822341982876. Available from: <http://journals.sagepub.com/doi/10.1177/117822341982876>
 27. Brandt J, Garne J, Tengrup I, Manjer J. Age at diagnosis in relation to survival following breast cancer: a cohort study. *World J Surg Oncol* [Internet]. 2015;13(1):33. Available from: <http://www.wjso.com/content/13/1/33>
 28. Love RR, Ba Duc N, Van Dinh N, Tu Quy T, Xin Y, Havighurst TC. Young Age as an Adverse Prognostic Factor in Premenopausal Women with Operable Breast Cancer. *Clin Breast Cancer* [Internet]. 2002 Jan;2(4):294–8. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1526820911704281>
 29. Dubsky PC, Gnant MFX, Taucher S, Roka S, Kandioler D, Pichler-Gebhard B, et al. Young Age as an Independent Adverse Prognostic Factor in Premenopausal Patients with Breast Cancer. *Clin Breast Cancer* [Internet]. 2002 Apr;3(1):65–72. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1526820911702452>
 30. Zhang X, Yang J, Cai H, Ye Y. Young age is an independent adverse prognostic factor in early stage breast cancer: a population-based study. *Cancer Manag Res* [Internet]. 2018 Sep;Volume 10:4005–18. Available from: <https://www.dovepress.com/young-age-is-an-independent-adverse-prognostic-factor-in-early-stage-b-peer-reviewed-article-CMAR>
 31. Chen H, Zhou M, Tian W, Meng K, He H. Effect of Age on Breast Cancer Patient Prognoses: A Population-Based Study Using the SEER 18 Database. Coleman WB, editor. *PLoS One* [Internet]. 2016 Oct 31;11(10):e0165409. Available from: <https://dx.plos.org/10.1371/journal.pone.0165409>
 32. Liu P, Li X, Mittendorf EA, Li J, Du XL, He J, et

- al. Comparison of clinicopathologic features and survival in young American women aged 18–39 years in different ethnic groups with breast cancer. *Br J Cancer* [Internet]. 2013 Sep 1;109(5):1302–9. Available from: <http://www.nature.com/articles/bjc2013387>
33. Azizah, A. M., Nor Saleha, I. T., Noor Hashimah, A., Asmah, Z., & Mastulu W. Malaysian National Cancer Registry Report 2012-2016 [Internet]. Malaysia: National Cancer Institute. 2017. Available from: <https://drive.google.com/file/d/1BuPWrb05N2Jez6sEP8VM5r6JtIIPN5W/view>
 34. Yip CH, Taib NAM, Mohamed I. Epidemiology of breast cancer in Malaysia. [Internet]. *Asian Pacific Journal of Cancer Prevention*. 2006. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/17059323>
 35. Mujar NMM, Dahlui M, Taib NA. Presentation, Diagnosis, and Treatment Among Patients With Breast Cancer in Malaysia. *J Glob Oncol* [Internet]. 2018 Oct;4(Supplement 3):25s-25s. Available from: <http://ascopubs.org/doi/10.1200/JGO.18.10280>
 36. Hisham AN, Yip C-H. Overview of Breast Cancer in Malaysian Women: A Problem with Late Diagnosis. *Asian J Surg* [Internet]. 2004 Apr;27(2):130–3. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1015958409603262>
 37. Mohd Mujar NM, Dahlui M, Emran NA, Abdul Hadi I, Wai YY, Arulanantham S, et al. Complementary and alternative medicine (CAM) use and delays in presentation and diagnosis of breast cancer patients in public hospitals in Malaysia. Lafrenie RM, editor. *PLoS One* [Internet]. 2017 Apr 27;12(4):e0176394. Available from: <https://dx.plos.org/10.1371/journal.pone.0176394>
 38. Mujar M, Dahlui M, Yip CH, Taib NA. Delays in time to primary treatment after a diagnosis of breast cancer: Does it impact survival? *Prev Med (Baltim)* [Internet]. 2013 Mar;56(3–4):222–4. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0091743512006032>
 39. Khan HMR, Saxena A, Gabbidon K, Rana S, Ahmed NU. Model-Based Survival Estimates of Female Breast Cancer Data. *Asian Pacific J Cancer Prev* [Internet]. 2014 Mar 30;15(6):2893–900. Available from: <http://koreascience.or.kr/journal/view.jsp?kj=POCPA9&py=2014&vnc=v15n6&sp=2893>
 40. Andre F, Slimane K, Bachelot T, Dunant A, Namer M, Barrelier A, et al. Breast Cancer With Synchronous Metastases: Trends in Survival During a 14-Year Period. *J Clin Oncol* [Internet]. 2004 Aug 15;22(16):3302–8. Available from: <http://ascopubs.org/doi/10.1200/JCO.2004.08.095>
 41. Walters S, Maringe C, Butler J, Rachet B, Barrett-Lee P, Bergh J, et al. Breast cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK, 2000-2007: a population-based study. *Br J Cancer* [Internet]. 2013 Mar 28;108(5):1195–208. Available from: <http://www.nature.com/articles/bjc20136>
 42. Gajdos C, Tartter PI, Bleiweiss IJ, Bodian C, Brower ST. Stage 0 to stage III breast cancer in young women¹¹No competing interests declared. *J Am Coll Surg* [Internet]. 2000 May;190(5):523–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S107275150000257X>
 43. Kroman N, Jensen MB, Wohlfahrt J, Mouridsen HT, Andersen PK, Melbye M. Factors influencing the effect of age on prognosis in breast cancer: Population based study. *Br Med J* [Internet]. 2000; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/10678859>
 44. Partridge AH, Hughes ME, Warner ET, Ottesen RA, Wong Y-N, Edge SB, et al. Subtype-Dependent Relationship Between Young Age at Diagnosis and Breast Cancer Survival. *J Clin Oncol* [Internet]. 2016 Sep 20;34(27):3308–14. Available from: <http://ascopubs.org/doi/10.1200/JCO.2015.65.8013>
 45. Hussein A, Khoury KE, Dbouk H, Khalil LE, Mouhieddine TH, El Saghir NS. Epidemiology and prognosis of breast cancer in young women [Internet]. *Journal of Thoracic Disease*. 2013. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/23819024>
 46. NBCF. About Breast Cancer: Types [Internet]. National Breast Cancer Foundation. 2019. Available from: <https://www.nationalbreastcancer.org/types-of-breast-cancer/>
 47. Shannon C, Smith IE. Breast cancer in adolescents and young women. *Eur J Cancer* [Internet]. 2003 Dec;39(18):2632–42. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/14642925>
 48. Boyle P. Triple-negative breast cancer: epidemiological considerations and recommendations. *Ann Oncol* [Internet]. 2012 Aug 1;23(suppl 6):vi7–12. Available from: <https://academic.oup.com/annonc/article-lookup/doi/10.1093/annonc/mds187>
 49. Erić I. Breast Cancer in Young Women: Pathologic and Immunohistochemical Features. *Acta Clin Croat* [Internet]. 2018 Sep;57(3):497–502. Available from: https://hrcak.srce.hr/index.php?show=clanak&id_clanak_jezik=315417
 50. Sabiani L, Houvenaeghel G, Heinemann M, Reyat F, Classe JM, Cohen M, et al. Breast cancer in young women: Pathologic features and molecular phenotype. *The Breast* [Internet]. 2016 Oct;29:109–16. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977616301163>
 51. Ribnikar D, Ribeiro JM, Pinto D, Sousa B, Pinto AC, Gomes E, et al. Breast Cancer Under Age 40: a Different Approach. *Curr Treat Options Oncol* [Internet]. 2015 Apr 22;16(4):16. Available from: <http://link.springer.com/10.1007/s11864-015-0334-8>
 52. Kwon J, Eom K-Y, Koo TR, Kim BH, Kang E, Kim S-W, et al. A Prognostic Model for Patients with Triple-Negative Breast Cancer: Importance of the Modified Nottingham Prognostic Index and Age. *J*

- Breast Cancer [Internet]. 2017;20(1):65. Available from: <https://synapse.koreamed.org/DOIx.php?id=10.4048/jbc.2017.20.1.65>
53. Geisler S, Demeter J, Perou CM, Lunning PE, Brown PO, Burren-Dale A-L, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A* [Internet]. 2003; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/12829800>
 54. van der Hage JA, Mieog JSD, van de Velde CJ, Putter H, Bartelink H, van de Vijver MJ. Impact of established prognostic factors and molecular subtype in very young breast cancer patients: pooled analysis of four EORTC randomized controlled trials. *Breast Cancer Res* [Internet]. 2011 Jun 24;13(3):R68. Available from: <https://breast-cancer-research.biomedcentral.com/articles/10.1186/bcr2908>
 55. Tang L-C, Jin X, Yang H-Y, He M, Chang H, Shao Z-M, et al. Luminal B subtype: A key factor for the worse prognosis of young breast cancer patients in China. *BMC Cancer* [Internet]. 2015 Dec 29;15(1):201. Available from: <http://bmccancer.biomedcentral.com/articles/10.1186/s12885-015-1207-z>
 56. Kwon JH, Kim YJ, Lee K-W, Oh D-Y, Park SY, Kim JH, et al. Triple negativity and young age as prognostic factors in lymph node-negative invasive ductal carcinoma of 1 cm or less. *BMC Cancer* [Internet]. 2010 Dec 15;10(1):557. Available from: <http://bmccancer.biomedcentral.com/articles/10.1186/1471-2407-10-557>
 57. Klauber-DeMore N. Tumor biology of breast cancer in young women. *Breast Dis* [Internet]. 23:9–15. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16823162>
 58. Azim HA, Partridge AH. Biology of breast cancer in young women. *Breast Cancer Res* [Internet]. 2014 Aug 27;16(4):427. Available from: <http://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-014-0427-5>
 59. Winslow S, Leandersson K, Edsju A, Larsson C. Prognostic stromal gene signatures in breast cancer. *Breast Cancer Res* [Internet]. 2015 Dec 21;17(1):23. Available from: <http://breast-cancer-research.biomedcentral.com/articles/10.1186/s13058-015-0530-2>
 60. Farmer P, Bonnefoi H, Anderle P, Cameron D, Wirapati P, Becette V, et al. A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. *Nat Med* [Internet]. 2009 Jan 4;15(1):68–74. Available from: <http://www.nature.com/articles/nm.1908>
 61. Narod SA. Breast cancer in young women. *Nat Rev Clin Oncol* [Internet]. 2012 Aug 26;9(8):460–70. Available from: <http://www.nature.com/articles/nrclinonc.2012.102>
 62. Arpino G, Pensabene M, Condello C, Ruocco R, Cerillo I, Lauria R, et al. Tumor characteristics and prognosis in familial breast cancer. *BMC Cancer* [Internet]. 2016 Dec 29;16(1):924. Available from: <http://bmccancer.biomedcentral.com/articles/10.1186/s12885-016-2962-1>
 63. Malone KE, Daling JR, Neal C, Suter NM, O'Brien C, Cushing-Haugen K, et al. Frequency of BRCA1/BRCA2 mutations in a population-based sample of young breast carcinoma cases. *Cancer* [Internet]. 2000 Mar 15;88(6):1393–402. Available from: <http://doi.wiley.com/10.1002/%28SICI%291097-0142%2820000315%2988%3A6%3C1393%3A%3AAID-CNCR17%3E3.0.CO%3B2-P>
 64. Evans JP, Skrzynia C, Susswein L, Harlan M. Genetics and the young woman with breast cancer. *Breast Dis* [Internet]. 2005; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/16823163>
 65. Peto J, Collins N, Barfoot R, Seal S, Warren W, Rahman N, et al. Prevalence of BRCA1 and BRCA2 Gene Mutations in Patients With Early-Onset Breast Cancer. *JNCI J Natl Cancer Inst* [Internet]. 1999 Jun 2;91(11):943–9. Available from: <https://academic.oup.com/jnci/article-lookup/doi/10.1093/jnci/91.11.943>
 66. Chen S, Parmigiani G. Meta-Analysis of BRCA1 and BRCA2 Penetrance. *J Clin Oncol* [Internet]. 2007 Apr 10;25(11):1329–33. Available from: <http://ascopubs.org/doi/10.1200/JCO.2006.09.1066>
 67. Hamdi Y, Soucy P, Kuchenbaecker KB, Pastinen T, Droit A, Lemazon A, et al. Association of breast cancer risk in BRCA1 and BRCA2 mutation carriers with genetic variants showing differential allelic expression: identification of a modifier of breast cancer risk at locus 11q22.3. *Breast Cancer Res Treat* [Internet]. 2017 Jan 28;161(1):117–34. Available from: <http://link.springer.com/10.1007/s10549-016-4018-2>
 68. Templeton AJ, Gonzalez LD, Vera-Badillo FE, Tibau A, Goldstein R, Šeruga B, et al. Interaction between Hormonal Receptor Status, Age and Survival in Patients with BRCA1/2 Germline Mutations: A Systematic Review and Meta-Regression. Brusgaard K, editor. *PLoS One* [Internet]. 2016 May 5;11(5):e0154789. Available from: <https://dx.plos.org/10.1371/journal.pone.0154789>
 69. Zhu Y, Wu J, Zhang C, Sun S, Zhang J, Liu W, et al. BRCA mutations and survival in breast cancer: an updated systematic review and meta-analysis. *Oncotarget* [Internet]. 2016 Oct 25;7(43):70113–27. Available from: <http://www.oncotarget.com/fulltext/12158>
 70. van den Broek AJ, Schmidt MK, van 't Veer LJ, Tollenaar RAEM, van Leeuwen FE. Worse Breast Cancer Prognosis of BRCA1/BRCA2 Mutation Carriers: What's the Evidence? A Systematic Review with Meta-Analysis. Adamovic T, editor. *PLoS One* [Internet]. 2015 Mar 27;10(3):e0120189. Available from: <https://dx.plos.org/10.1371/journal.pone.0120189>
 71. Dahlui M, Ramli S, Bulgiba AM. Breast cancer

- prevention and control programs in Malaysia. *Asian Pac J Cancer Prev* [Internet]. 2011;12(6):1631–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/22126511>
72. Vieira R, Biller G, Uemura G, Ruiz C, Curado M. Breast cancer screening in developing countries. *Clinics* [Internet]. 2017 Apr 10;72(4):244–53. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5401614/?report=classic>
 73. Siu AL. Screening for Breast Cancer: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med* [Internet]. 2016 Feb 16;164(4):279. Available from: <http://annals.org/article.aspx?doi=10.7326/M15-2886>
 74. Panieri E. Breast cancer screening in developing countries. *Best Pract Res Clin Obstet Gynaecol* [Internet]. 2012 Apr;26(2):283–90. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1521693411001714>
 75. Yip CH, Pathy NB, Teo SH. A review of breast cancer research in Malaysia [Internet]. *Medical Journal of Malaysia*. 2014. Available from: <https://www.ncbi.nlm.nih.gov/pubmed/25417947>
 76. Poggio F, Lambertini M, Bighin C, Conte B, Blondeaux E, D'Alonzo A, et al. Management of young women with early breast cancer. *ESMO Open* [Internet]. 2018 Nov 14;3(Suppl 1):e000458. Available from: <http://esmoopen.bmj.com/lookup/doi/10.1136/esmoopen-2018-000458>
 77. Paluch-Shimon S, Pagani O, Partridge AH, Abulkhair O, Cardoso M-J, Dent RA, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). *The Breast* [Internet]. 2017 Oct;35:203–17. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977617305489>
 78. Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in Risk Factors for Local and Distant Recurrence After Breast-Conserving Therapy or Mastectomy for Stage I and II Breast Cancer: Pooled Results of Two Large European Randomized Trials. *J Clin Oncol* [Internet]. 2001 Mar 15;19(6):1688–97. Available from: <http://ascopubs.org/doi/10.1200/JCO.2001.19.6.1688>
 79. Vila J, Gandini S, Gentilini O. Overall survival according to type of surgery in young (≤ 40 years) early breast cancer patients: A systematic meta-analysis comparing breast-conserving surgery versus mastectomy. *The Breast* [Internet]. 2015 Jun;24(3):175–81. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S096097761500017X>
 80. Pathy NB, Verkooijen HM, Taib NA, Hartman M, Yip CH. Impact of breast surgery on survival in women presenting with metastatic breast cancer. *Br J Surg* [Internet]. 2011 Nov;98(11):1566–72. Available from: <http://doi.wiley.com/10.1002/bjs.7650>
 81. Agarwal S, Pappas L, Neumayer L, Kokeny K, Agarwal J. Effect of Breast Conservation Therapy vs Mastectomy on Disease-Specific Survival for Early-Stage Breast Cancer. *JAMA Surg* [Internet]. 2014 Mar 1;149(3):267. Available from: <http://archsurg.jamanetwork.com/article.aspx?doi=10.1001/jamasurg.2013.3049>
 82. Maishman T, Cutress RI, Hernandez A, Gerty S, Copson ER, Durcan L, et al. Local Recurrence and Breast Oncological Surgery in Young Women With Breast Cancer. *Ann Surg* [Internet]. 2017 Jul;266(1):165–72. Available from: <http://journals.lww.com/00000658-201707000-00024>
 83. Pritchard KI. Adjuvant therapy of the very young woman. *The Breast* [Internet]. 2007;16:136–46. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977607001464>
 84. Meattini I, Lambertini M, Desideri I, De Caluwā A, Kaidar-Person O, Livi L. Radiation therapy for young women with early breast cancer: Current state of the art. *Crit Rev Oncol Hematol* [Internet]. 2019 May;137:143–53. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S104084281830430X>
 85. Freedman RA, Partridge AH. Management of breast cancer in very young women. *The Breast* [Internet]. 2013 Aug;22:S176–9. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S0960977613001690>
 86. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol* [Internet]. 2010 Dec;11(12):1135–41. Available from: <https://linkinghub.elsevier.com/retrieve/pii/S1470204510702576>
 87. daCosta DiBonaventura M, Copher R, Basurto E, Faria C, Lorenzo R. Patient preferences and treatment adherence among women diagnosed with metastatic breast cancer. *Am Heal drug benefits* [Internet]. 2014 Oct;7(7):386–96. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25525495>
 88. Kim I, Park S, Hwang H, Lee JS, Ko SM, Kim S II, et al. Clinical Significance of Age at the Time of Diagnosis among Young Breast Cancer Patients. *J Breast Cancer* [Internet]. 2011;14(4):314. Available from: <https://synapse.koreamed.org/DOIx.php?id=10.4048/jbc.2011.14.4.314>
 89. McCowan C, Wang S, Thompson AM, Makubate B, Petrie DJ. The value of high adherence to tamoxifen in women with breast cancer: a community-based cohort study. *Br J Cancer* [Internet]. 2013 Sep 15;109(5):1172–80. Available from: <http://www.nature.com/articles/bjc2013464>
 90. Narod SA. Compliance With Tamoxifen in Women With Breast Cancer and a BRCA1 or BRCA2 Mutation. *J Clin Oncol* [Internet]. 2010 Nov 20;28(33):e698–9. Available from: <http://ascopubs.org/doi/10.1200/JCO.2010.31.5770>

91. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. *Breast Cancer Res Treat* [Internet]. 2011 Apr 28;126(2):529–37. Available from: <http://link.springer.com/10.1007/s10549-010-1132-4>
92. Huiart L, Ferdynus C, Giorgi R. A meta-regression analysis of the available data on adherence to adjuvant hormonal therapy in breast cancer: summarizing the data for clinicians. *Breast Cancer Res Treat* [Internet]. 2013 Feb 12;138(1):325–8. Available from: <http://link.springer.com/10.1007/s10549-013-2422-4>
93. Murphy CC, Bartholomew LK, Carpentier MY, Bluethmann SM, Vernon SW. Adherence to adjuvant hormonal therapy among breast cancer survivors in clinical practice: a systematic review. *Breast Cancer Res Treat* [Internet]. 2012 Jul 12;134(2):459–78. Available from: <http://link.springer.com/10.1007/s10549-012-2114-5>
94. Lambertini M, Viglietti G, de Azambuja E. Controversies in oncology: which adjuvant endocrine therapy is to be given to premenopausal patients with hormone receptor-positive breast cancer? *ESMO Open* [Internet]. 2018 Mar 29;3(3):e000350. Available from: <http://esmoopen.bmj.com/lookup/doi/10.1136/esmoopen-2018-000350>