

Practical consensus recommendation on when to do BRCA testing

Purvish M. Parikh, J. Wadhwa¹, S. Minhas², A. Gupta³, S. Mittal⁴, S. Ranjan⁵, P. Mehta⁶, R. Singh⁷, S. P. Kataria⁸, S. Salim⁹, M. Ahmed¹⁰, S. Aggarwal²

Abstract

BRCA-mutation associated breast cancer and to future cancer risks and sensitivity to systemic therapies. Now that rapid genetic testing for BRCA1 and BRCA2 mutations is available, BRCA mutation status can be considered when making treatment and prevention decisions for BRCA testing, BRCA mutation carriers with breast cancer. Expert group used data from published literature, practical experience, and opinion of a large group of academic oncologists, to arrive at practical consensus recommendations for use by the community oncologists.

Key words: 40 years, age, extended germline mutation, family history, ovarian cancer, pancreatic, paternal history, prostate

Introduction

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discuss about when to go for BRCA testing in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.^[1,2] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr Shsd Salim and Dr S.P.Katria whereas the discussions were moderated by Dr Jyoti Wadhwa and Dr Purvish Parikh. The core expert group consists of Dr Ashutosh Gupta, Dr Sushant Mittal, Dr Prashant Mehta, Dr Christopher Twelves, Dr Randeep Singh and Dr Sarah P Cate. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use BRCA testing in Breast cancer patients.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.^[3-5] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their ersonal experiences, make comments and record dissent while voting for the consensus

statements. Total of five broad question categories were part of the expert group discussions [Table 1].

This manuscript is the outcome of the expert group consensus arrived at on Saturday, May 20th, 2017.

Breast cancer is the commonest cancer of urban Indian women and the second commonest in the rural women.^[4] Owing to the lack of awareness of this disease and in absence of a breast cancer screening program, the majority of breast cancers are diagnosed at a relatively advanced stage. The quality of care available for breast cancer patients varies widely according to where the patient is treated. Although there are some centers of excellence providing multimodality protocol-based treatment at par with the best anywhere in the world, the vast majority of breast cancer patients undergo inadequate and inappropriate treatment due to lack of high-quality infrastructure and sometimes skills, and above all financial resources. The recent emphasis on health education, early diagnosis of cancers, and more public facilities for cancer treatment are expected to bring about the much needed improvement in breast cancer care in India. Over 100,000 new breast cancer patients are estimated to be diagnosed annually in India.^[5,6] As per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries of Delhi, Mumbai, Ahmedabad, Calcutta, and Trivandrum where it constitutes >30% of all cancers in females.^[7] In the rural PBCR of Barshi, breast cancer is the second commonest cancer in women after cancer of the uterine cervix.^[7] The age standardized incidence rates (AARs) range from 6.2 to 39.5 per 100,000 Indian women. The rise in incidence of 0.5–2% per annum has been seen across all regions of India and in all age groups but more so in the younger age groups (<45 years).^[8] In general, breast cancer has been reported to occur a decade earlier in Indian patients compared to their western counterparts.

Familial and genetic breast cancer in Indian women

Almost a third of all breast cancer patients are believed to have familial disease pattern, and some 5% are believed to be hereditary, with the BRCA1 and BRCA2 gene mutations having been identified as the major genetic causes.^[2,9-18] In an Indian study on 226 breast cancer patients, 20.7% had a

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Department of Oncology, Shalby Cancer and Research Institute, Mumbai, Maharashtra, ¹Department of Medical Oncology, Medanta Hospital, ²Department of Medical Oncology, Artemis Hospital, Gurugram, ³Department of Medical Oncology, Asian Institute of Medical Sciences, Faridabad, Haryana, ⁴Department of Medical Oncology, Sir Ganga Ram Hospital, ⁵Department of Radiation Oncology, Safdarjung Hospital, ⁶Department of Medical Oncology, Action Balajee Cancer Center, ⁷Department of Medical Oncology, Safdarjung Hospital, New Delhi, ⁸Department of Medicine, INHS Sanjivani, Kochi, Kerala, ⁹Department of Oncology, Hakim Sanaullah Cancer Center, Baramulla, Jammu and Kashmir, ¹⁰Department of Radiation Oncology, Jolly Grant Himalayan Institute, Dehradun, Uttarakhand, India

Correspondence to: Dr. Purvish M. Parikh, E-mail: purvish1@gmail.com

positive family history.^[18] On the contrary, numerous other studies have reported a low rate of familial pattern of breast cancer in Indian patients. This is particularly interesting given the relatively young age of Indian breast cancer patients.^[12,14,16,18] Genetic screening/diagnosis is not routinely performed in most Indian center due to paucity of funds and facilities. As a result, there is scarce data on the genetic composition and BRCA1/2 mutations in Indian patients. The available studies hint at a rather low incidence of BRCA mutations. In most populations, 6–10% of patients with breast cancer have mutation in BRCA gene irrespective of their family history. Though there are no robust figures, various Indian studies have reported BRCA mutations in 9–25% of familial breast cancer cases.^[19-23] Hedau *et al.*^[24] demonstrated 3 novel BRCA1 mutations including a founder Ashkenazi Jewish BRCA1 mutation in Indian breast cancer patients.^[24]

At the present, there are no formal Indian guidelines stating which patients should be referred for genetic risk evaluation at the time of breast cancer diagnosis; however standard criteria for referral for genetic risk evaluation have been applied to this population.^[25] In general, women with at least a 10% likelihood of carrying a *BRCA* mutation have been included in studies of peri-diagnostic genetic testing to date.^[24,26,27] Certainly, high risk women for whom surgical treatment decisions could be impacted by genetic test results should be considered for peri-diagnostic genetic risk evaluation.

Impact of *BRCA* mutation status on local therapy for breast cancer

When considering options for local therapy for *BRCA* mutation-associated breast cancer, several issues come into play. Questions arise about the efficacy of breast conserving therapy and the possibility of excess toxicity of radiation in mutation carriers. Additionally, given the high rate of contralateral breast cancer, mutation carriers with newly diagnosed breast cancer may choose to incorporate breast cancer prevention into their surgical management and undergo mastectomy for the affected side plus contralateral prophylactic mastectomy. This section reviews issues related to management of the affected breast and options for the contralateral breast.

To the question regarding the BRCA testing in all breast cancers under age 40 years? The expert panel did not agree to be equally divided votes that are 50%-50% by the delegate shows [Table 2]. Half of the voters were in favor of BRCA testing in all breast cancers under age 40 years and remaining half do not support it, The expert panel members agreed that it is established standard of care to do BRCA testing in all patients with breast cancer diagnosed at or below the age of 40, as specified in NCCN guidelines.^[25] This was followed diligently in the USA whereas in the UK the cut off age as 50 years of age. In India, factors responsible for not adhering to these guidelines include cost of testing and insufficient trained counseling professionals. Other factors discussed like reproductive history, family history and understand legality should not prevent the community oncologist from discussing or recommending BRCA testing.

A clear majority of delegates polled 66% votes in favor of BRCA testing for sporadic post menopausal triple negative breast cancer 55 years [Table 3], The expert panel also agreed

on age cut off 60 years for such a scenario and commented that it's also has implication on type of treatment given to patient so it's important in such patients to advise for BRCA testing.

Absolute majority of delegates polled 100% votes and expert panel are in favor of extending germline mutation testing in triple negative 35 year old female [Table 4]. The expert panel recommending on doing such a testing as not to miss out number of other syndromes. And also suggested to chose lab wisely.

This time also a clear majority of delegates polled 71% votes in favor of BRCA testing for post menopausal breast cancer 60 years old with one maternal cousin having ovarian cancer [Table 5]. The expert panel opinion was also in favor. And one expert from US suggested for NCCN guidelines.^[25] And one of expert also suggested using risk assessment calculators in such setting.

Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Question 1 - Will you do BRCA testing in all breast cancers under age 40 years?
Question 2 - Will you do BRCA testing for sporadic postmenopausal triple negative breast cancer 55 years?
Question 3 - Will you go for extended germline mutation testing in triple negative 35-year-old female?
Question 4 - Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer?
Question 5 - Will you do BRCA testing for postmenopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer?

Update in oncology-X-2017

Table 2: Question 1 - Will you do BRCA testing in all breast cancers under age 40 years?

Options (%)	Yes	No
Percentage of polled oncologists	50	50

Expert group consensus: The expert panel recommended not to do BRCA testing in all breast cancers under the age of 40 years

Table 3: Question 2 - Will you do BRCA testing for sporadic post menopausal triple negative breast cancer 55 years?

Options (%)	Yes	No
Percentage of polled oncologists	66	34

Expert group consensus: BRCA testing should be done for all breast cancer patients above the age of 60 years

Table 4: Question 3 - Will you go for extended germline mutation testing in triple negative 35-year-old female?

Options (%)	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Extended germline mutation testing (beyond BRCA) should be done fore triple negative young patients with breast cancer so as not to miss out on other syndromes

Table 5: Question 4 - Will you do BRCA testing for postmenopausal breast cancer 60 years old with one maternal cousin having ovarian cancer?

Options (%)	Yes	No
Percentage of polled oncologists	71	29

Expert group consensus: The expert panel recommended BRCA testing in breast cancer patients with maternal family history of ovarian cancer

Table 6: Question 5 - Will you do BRCA testing for postmenopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer?

Options (%)	Yes	No
Percentage of polled oncologists	85	15

Expert group consensus: BRCA testing is recommended in selected cases with breast cancer who have paternal family history of prostate or pancreatic cancer (based on published guidelines)

Absolute majority of delegates voted in favor of BRCA test for post menopausal breast cancer 60 years with one paternal cousin having prostate cancer or pancreatic cancer [Table 6]. The expert panelist agree if facilities are available and patient qualifies for the test based on guidelines, then it should be definitely discussed with the patient and the genetic counseling is very important for genetic testing.

Conclusion

The update in oncology-X-2017 expert group for challenging common case scenarios in Breast Cancer had the specific mandate to develop practical consensus Recommendations PCR for easy application by the community oncologist. It took into consideration data as well as the current practices in India, in addition to international data that conventional panels look at, making it the perfect blend of evidence, clinical expertise, and real life preference.

The options for BRCA testing in breast cancer patients or the management of *BRCA* mutation-associated breast cancer is complex and multiple factors regarding the cancer at hand and future cancer risks must be weighed together when making treatment decisions. With the availability of peri-diagnostic genetic testing, care plans which incorporate *BRCA* mutation status can now be developed. Breast health specialists, genetic counselors, gynecologic oncologists, and primary health care physicians all have an important role in discussing risk-reduction strategies with women at very high risk of breast and ovarian cancer. Evaluating patient risk factors and obtaining a comprehensive family history are important steps in assessing breast and ovarian cancer risks. Genetic testing can identify individuals at very high risk for hereditary breast and ovarian cancer. Evidence is accumulating, and efficacy data are currently available for some, but not all, medical interventions for *BRCA1* and *BRCA2* mutation carriers. A coordinated team effort can provide a supportive environment and personalized approach for patients facing difficult surgical vs nonsurgical decisions related to management of hereditary breast and ovarian cancer. With time, these and other questions will be answered and we will become better able to individually tailor treatment and prevention plans for women with *BRCA* mutation-associated breast cancer.

Discussion

Traditionally, decisions regarding systemic therapy for *BRCA* mutation-associated breast cancer have been made based on the characteristics of the disease and not on the *BRCA* mutation status. However, this may change as questions exist regarding the impact of mutation status on prognosis and recent data suggesting unique patterns of sensitivity and resistance to systemic therapies in *BRCA* mutation-associated breast cancer emerges.^[28-30] Notably, *BRCA* mutation-associated breast cancers

appear to be particularly sensitive to a new class of drugs which inhibit poly (ADP-Ribose) polymerase (PARP).^[28-30]

Since genetic testing was introduced, its use for risk assessment by health care professionals has been escalating. Hereditary *BRCA1* and *BRCA2* mutations account for about 60% of inherited breast cancer and are the only known causes of hereditary breast and ovarian cancer syndrome. Women with a germline mutation in *BRCA1* or *BRCA2* or a hereditary predisposition for breast cancer have markedly increased risk of early-onset breast cancer and ovarian cancer.

Approximately 80% of breast and 90% of ovarian cancer cases are thought to be sporadic with no associated family history. Multifactorial familial risk accounts for approximately 10% to 15% of breast cancer. In the future, testable panels of genetic variants likely will combine to subtly alter risk. Hereditary breast cancer—cancer attributable to a single hereditary gene mutation in either *BRCA1* or *BRCA2*—accounts for approximately 5% of breast cancer cases, characteristically occurring before age 50 years. Approximately 4% to 11% of ovarian cancer is attributable to a germline mutation, with the greatest proportions in cancers diagnosed before age 50 years.^[31] An estimated 1 in 300 to 1 in 800 US individuals are *BRCA* carriers (1 in 50 individuals with Ashkenazi Jewish heritage).^[32,33] Hereditary breast and ovarian cancer attributed to a mutation in a particular gene (ie, *BRCA1* or *BRCA2*) can be passed on to the next generation, transmitted in an autosomal dominant pattern. The gene mutation may originate from the maternal or the paternal side, and each offspring of a *BRCA* carrier has a 50% chance of inheriting the mutation.^[34,35]

Take Home Messages

- 1 The expert panel recommended not to do BRCA testing in all breast cancers under the age of 40 years
- 2 BRCA testing should be done for all breast cancer patients above the age of 60 years.
- 3 Extended germline mutation testing (beyond BRCA) should be done for triple negative young patients with breast cancer so as not to miss out on other syndromes.
- 4 The expert panel recommended BRCA testing in breast cancer patients with maternal family history of ovarian cancer.
- 5 BRCA testing is recommended in selected cases with breast cancer who have paternal family history of prostate or pancreatic cancer (based on published guidelines)

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Conflicts of interest

There are no conflicts of interest.

References

1. National Cancer Registry Programme, Indian Council of Medical Research. Leading sites of cancer. In: Consolidated Report of Population Based Cancer Registries 20012004, Incidence and Distribution of Cancer. Bangalore: Coordinating Unit, National Cancer Registry Programme (ICMR); 2006. p. 8-30.
2. Badwe RA, Gangawal S, Mittra I, Desai PB. Clinico-pathological features and prognosis of breast cancer in different religious communities in India. *Indian J Cancer* 1990;27:220-8.
3. Altekruse SF, Kosary CL, Krapcho M, editors. SEER Cancer Statistics Review. National Cancer Institute; 19752007.
4. National Cancer Registry Program. Ten Year Consolidated Report of the Hospital Based Cancer Registries, 1984–1993, An Assessment of the Burden and Care of Cancer Patients. New Delhi: Indian Council of Medical Research; 2001.

5. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. *World J Surg* 2007;31:1031-40.
6. Chopra R. The Indian scene. *J Clin Oncol* 2001;19 18 Suppl: 106S-11S.
7. Aggarwal V, Agarwal G, Lal P, Krishnani N, Mishra A, Verma AK, *et al.* Feasibility study of safe breast conservation in large and locally advanced cancers with use of radiopaque markers to mark pre-neoadjuvant chemotherapy tumor margins. *World J Surg* 2008;32:2562-9.
8. Murthy NS, Agarwal UK, Chaudhry K, Saxena S. A study on time trends in incidence of breast cancer – Indian scenario. *Eur J Cancer Care (Engl)* 2007;16:185-6.
9. de Waard F. Breast cancer incidence and nutritional status with particular reference to body weight and height. *Cancer Res* 1975;35:3351-6.
10. Gajalakshmi CK, Shanta V. Risk factors for female breast cancer. A hospital-based case-control study in Madras, India. *Acta Oncol* 1991;30:569-74.
11. Jussawalla DJ, Yeole BB, Natekar MV. Histological and epidemiological features of breast cancer in different religious groups in greater Bombay. *J Surg Oncol* 1981;18:269-79.
12. Jussawalla DJ, Jain DK. Breast cancer and religion in greater Bombay women: An epidemiological study of 2130 women over a 9-year period. *Br J Cancer* 1977;36 Suppl 5:634-8.
13. Jussawalla DJ, Yeole BB, Natekar MV, Narayan RA. Epidemiology of breast cancer in India. *Indian J Cancer* 1975;12:231-42.
14. Rao DN, Ganesh B. Estimate of cancer incidence in India in 1991. *Indian J Cancer* 1998;35 Suppl 1:10-8.
15. Rao DN, Ganesh B, Desai PB. Role of reproductive factors in breast cancer in a low-risk area: A case-control study. *Br J Cancer* 1994;70:129-32.
16. Rao DN, Dinshaw KA. Epidemiological Review: In Risk Factors and Survival Rates. Mumbai: Hospital Cancer Registry, Division of Epidemiology and Biostatistics, Tata Memorial Hospital; 1999. p. 1-7.
17. Anderson DE. Some characteristics of familial breast cancer. *Cancer* 1971;28 Suppl 6:1500-4.
18. Saxena S, Rekhi B, Bansal A, Bagga A, Chintamani, Murthy NS, *et al.* Clinico-morphological patterns of breast cancer including family history in a New Delhi hospital, India – a cross-sectional study. *World J Surg Oncol* 2005;3:67.
19. Valarmathi MT, A A, Deo SS, Shukla NK, Das SN. BRCA1 germline mutations in Indian familial breast cancer. *Hum Mutat* 2003;21:98-9.
20. Kumar BV, Lakhotia S, Ankathil R, Madhavan J, Jayaprakash PG, Nair MK, *et al.* Germline BRCA1 mutation analysis in Indian breast/ovarian cancer families. *Cancer Biol Ther* 2002;1:18-21.
21. Rajkumar T, Soumitra N, Nancy NK, Swaminathan R, Sridevi V, Shanta V, *et al.* BRCA1, BRCA2 and CHEK2 (1100 del C) germline mutations in hereditary breast and ovarian cancer families in South India. *Asian Pac J Cancer Prev* 2003;4:203-8.
22. Hedau S, Jain N, Husain SA, Mandal AK, Ray G, Shahid M, *et al.* Novel germline mutations in breast cancer susceptibility genes BRCA1, BRCA2 and p53 gene in breast cancer patients from India. *Breast Cancer Res Treat* 2004;88:177-86.
23. Tercyak KP, Peshkin BN, Brogan BM, DeMarco T, Pennanen MF, Willey SC, *et al.* Quality of life after contralateral prophylactic mastectomy in newly diagnosed high-risk breast cancer patients who underwent BRCA1/2 gene testing. *J Clin Oncol* 2007;25:285-91.
24. Valarmathi MT, Sawhney M, Deo SS, Shukla NK, Das SN. Novel germline mutations in the BRCA1 and BRCA2 genes in Indian breast and breast-ovarian cancer families. *Hum Mutat* 2004;23:205.
25. Genetic/Familial High-Risk Assessment: Breast and Ovarian. NCCN Guidelines version 1; 2011. Available from: <http://www.nccn.org>.
26. Schwartz MD, Lerman C, Brogan B, Peshkin BN, Isaacs C, DeMarco T, *et al.* Utilization of BRCA1/BRCA2 mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiol Biomarkers Prev* 2005;14:1003-7.
27. Wevers MR, Ausems MG, Verhoef S, Bleiker EM, Hahn DE, Hogervorst FB, *et al.* Behavioral and psychosocial effects of rapid genetic counseling and testing in newly diagnosed breast cancer patients: Design of a multicenter randomized clinical trial. *BMC Cancer* 2011;11:6.
28. Frost MH, Slezak JM, Tran NV, Williams CI, Johnson JL, Woods JE, *et al.* Satisfaction after contralateral prophylactic mastectomy: The significance of mastectomy type, reconstructive complications, and body appearance. *J Clin Oncol* 2005;23:7849-56.
29. Carey LA, Sharpless NE. PARP and cancer – if it's broke, don't fix it. *N Engl J Med* 2011;364:277-9.
30. Gartner EM, Burger AM, Lorusso PM. Poly (adp-ribose) polymerase inhibitors: A novel drug class with a promising future. *Cancer J* 2010;16:83-90.
31. Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Kwan E, *et al.* Prevalence and penetrance of germline BRCA1 and BRCA2 mutations in a population series of 649 women with ovarian cancer. *Am J Hum Genet* 2001;68:700-10.
32. ACOG. The American Congress of Obstetricians and Gynecologists. Washington, DC: American Congress of Obstetricians and Gynecologists. Available from: http://www.acog.org/from_home/proxy/. [Last accessed on 2010 Sep 20].
33. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. *Nat Rev Cancer* 2004;4:665-76.
34. Jatoti I, Anderson WF. Management of women who have a genetic predisposition for breast cancer. *Surg Clin North Am* 2008;88:845-61, vii-viii.
35. Parikh PM, Gupta S, Parikh B, Smruti BK, Issrani J, Topiwala S, *et al.* Management of primary and metastatic triple negative breast cancer: Perceptions of oncologists from India. *Indian J Cancer* 2011;48:158-64.

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