The THAI Journal of SURGERY 2024;45(2):57-62.
Official Publication of The Royal College of Surgeons of Thailand

Case Report

Identification of a Pathogenic Germline Variant in the BRCA2 Gene in a Patient Diagnosed with Ductal Carcinoma in Situ (DCIS): A Case Report and Review of the Literature

Panupong Sukpan, MD[1,2]
Kanyanatt Kanokwiroon, PhD[1]
Surasak Sangkhathat, MD, PhD[3]

[1] *Department of Biomedical Sciences and Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
[2] *Surgery Department, Medical Education Center, Naradhiwas Rajanagarindra Hospital, Narathiwat, Thailand*
[3] *Translational Medicine Research Center, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkhla, Thailand*

Abstract Advances in sequencing technology are rapidly progressing, leading to reduced costs and enhanced accessibility to genetic testing for cancers. Thailand, classified as a middle-income nation, integrates Universal Coverage of public health insurance to encompass germline genetic testing for breast cancer (BC) patients and their relatives who are at high risk of Hereditary Breast and Ovarian Cancer Syndrome (HBOC). In this study, we describe the case of a 48-year-old woman diagnosed with Ductal Carcinoma in Situ (DCIS) who underwent genetic testing, which revealed the presence of a pathogenic germline variant in the *BRCA2* gene. The test was also conducted on three children. The findings indicate that two of three children carry pathogenic germline variants similar to those identified in their mother. The patient and their family members, who presented with both inherited and non-inherited *BRCA2* germline mutations, underwent counseling sessions delivered by certified genetic counselors. Moreover, implementing cancer surveillance and risk reduction strategies for individuals with inherited *BRCA2* germline mutations, encompassing BC, ovarian cancer, prostate cancer, pancreatic cancer, and malignant melanoma, offers significant advantages for this familial cohort.

Keywords: Breast cancer, Germline mutation, *BRCA*

Introduction

The etiology of Hereditary Breast And Ovarian Cancer Syndrome (HBOC) frequently involves the presence of deleterious germline mutations within the *BRCA1/2* genes.[1] The presence of the *BRCA2* pathogenic germline variants has been associated with a projected cumulative risk of 45% for breast cancer (BC) and 11% for ovarian cancer by age 70.[2] Undertaking a risk-reducing bilateral salpingo-oophorectomy and a mastectomy yields a pronounced diminution in the susceptibility to cancer.[3] The administration of Olaparib, a Poly ADP-Ribose Polymerase (PARP) inhibitor, demonstrates enhanced survival outcomes in individuals with locally advanced or metastatic BC who harbor *BRCA* germline mutations.[4] Germline genetic testing confers a plethora of advantageous outcomes for individuals diagnosed with BC.[5]

We present herein a case study detailing the condition of a 48-year-old Thai woman affected with ductal carcinoma in situ (DCIS) of the breast. It is noteworthy

Received for publication 11 March 2024; Revised 15 May 2024; Accepted 30 May 2024

Corresponding author: Surasak Sangkhathat, MD, PhD Translational Medicine Research Center, Faculty of Medicine, Prince of Songkla University, Hatyai, Songkhla, Thailand; Email: surasak.sa@psu.ac.th;Telephone: +66 7 445 1180

that the patient harbored a *BRCA2* pathogenic germline variant, which has been subsequently transmitted to two out of her three offspring.

Case Presentation

A woman 48 years of age presented with a discernible mass in the outermost region of the upper left breast. She had not observed any changes in the lump size and had not previously encountered any associated discomfort. The physical examination revealed a palpable irregularity characterized by a 4-cm firm consistency mass located in the upper outer quadrant of the left breast and fixed to the surrounding tissue. Additional physical examinations showed an absence of nipple discharge and no palpable lymph nodes, including those in the axillary region. Other examinations were unremarkable. The patient negated any history of underlying medical conditions and denied the presence of cancer in her family, particularly breast and ovarian malignancies (Figure 1).

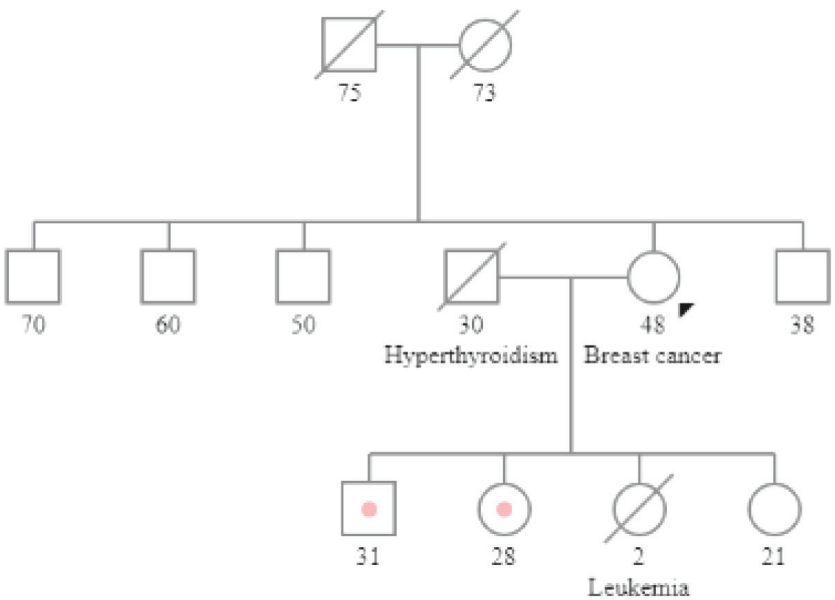

Figure 1 Pedigree of the family with a germline *BRCA2* mutation

The radiological assessment of both breasts reveals an irregular hypodense mass in the left breast's upper outer region, measuring 1.4 × 4.6 × 5.4 cm in dimensions. Due to the potential risk of BC, the physician conducted a biopsy utilizing a core needle biopsy technique for subsequent histopathological examination, which reported DCIS.

Following a thorough consultation, the patient made the informed decision to undergo a left mastectomy, opting not to conserve her breast. The patient underwent a left mastectomy accompanied by a sentinel lymph node biopsy. The postoperative pathological findings indicate the absence of any margin involvement in high-grade DCIS and no evidence of metastasis in all four nodes examined. The immunohistochemical analysis of examination results revealed the tumor to be estrogen receptor (ER) positive, progesterone receptor (PR) negative, human epidermal growth factor receptor 2 (HER2) negative, with a Ki-67 proliferation index of 35%. Tamoxifen at a daily dosage of 20 mg is administered post-surgery to mitigate the risk of invasive BC in the patient.

The patient underwent germline genetic testing utilizing Next-Generation Sequencing (NGS) technology, specifically a panel test encompassing multiple genes. She underwent pretest counseling facilitated by individuals who have completed training in genetic counseling and obtained certification through the Training Curriculum in Genetic Counseling. After verification through the standard dideoxynucleotide test (Sanger sequencing). The germline genetic testing results indicate the patient harbored a germline mutation in the *BRCA2* gene. The mutation involved a deletion of two bases, leading to

a frameshift mutation identified as NM_000059.4(BRCA2):c.3680_3681del, rs80359395, NP_000050.3:p.Leu1227fs. The Sanger sequencing technique was employed to conduct germline genetic testing on all three offspring of the patient. Each of the three children underwent pre-test and post-test genetic counseling. The results of germline genetic testing indicated that one son and one daughter are carriers of the *BRCA2* mutation, whereas the youngest daughter exhibits a wild-type genetic profile (Figure 2). The daughter, with the wild-type genotype, is advised that she had an ordinary susceptibility risk to cancer development.

Figure 2 The Sanger sequencing outcomes for the patient's familial genetic analysis.
A: A 47-year-old female diagnosed with breast cancer (index patient). A 30-year-old son., A 27-year-old daughter. B: A 20-year-old daughter (Wild type).

The strategic handling of a BC patient extended to the comprehensive management of a familial case involving both a male and female offspring, each harboring the *BRCA2* pathogenic germline variant. Guidance for individuals and their familial counterparts harboring the *BRCA2* germline mutation was formulated in accordance with the recommendations delineated in the 2024 edition of The National Comprehensive Cancer Network (NCCN) guidelines. All family members who underwent genetic counseling and *BRCA* testing were recommended to adopt lifestyle modifications aimed at reducing their risk of cancer. Recommendations for individuals encountering DCIS at the age of 48 involve undergoing contralateral risk-reduction mastectomy along with risk-reducing salpingo-oophorectomy. Despite the patient's refusal of surgical intervention, the suggested course of action entails the implementation of an annual mammogram and breast Magnetic Resonance Imaging (MRI) screening for the unaffected breast. In the case of a 28-year-old daughter bearing the *BRCA2* mutation, a regimen of annual breast MRI screenings has been initiated, yielding consistently negative results. The discussion regarding risk-benefit analysis concerning the utilization of risk-reducing interventions like bilateral

mastectomy and bilateral salpingo-oophorectomy following childbirth necessitates meticulous consideration. In the case of a 31-year-old male with a *BRCA2* germline mutation, it is advisable to commence a routine of breast self-examination and clinical breast examination every 12 months, initiating the screenings at the age of 35 years. Prostate cancer screening is advised, encompassing an annual prostate-specific antigen (PSA) test commencing at the age of 40. For individuals harboring the *BRCA2* germline mutation, the initiation of pancreatic cancer screening is recommended at the age of 50 years. Modalities such as MRI, magnetic resonance cholangiopancreatography (MRCP), and/or endoscopic ultrasound (EUS) are indicated for comprehensive screening. Melanoma poses an elevated risk, notwithstanding the absence of screening programs advocating. It is advised to refrain from ultraviolet exposure.

Discussion

BRCA2 plays a crucial role in DNA repair, and mutations in this gene impart a substantially elevated lifetime risk of BC, typically ranging from 50% to 80%.[6] The *BRCA2* germline mutation associated with HBOC has documented over 3,400 variants classified as pathogenic mutations.[7] Not only linked to breast and ovarian cancers, mutations of *BRCA2* also to other malignancies, including those affecting the pancreas, prostate, and melanoma[8] The biallelic *BRCA2* germline mutation results in Fanconi anemia syndrome, an uncommon genetic disorder that impacts the bone marrow and escalates the susceptibility to hematologic malignancies.[9] A familial member is dead of a hematologic malignancy at the age of two. Yet, the available data does not substantiate the association of Fanconi anemia as the causative factor for the malignancy.

Since 2013, the prevalence of *BRCA1/2* genetic testing has experienced a notable surge attributed to what has become known as the Angelina Jolie Effect.[10] Furthermore, there has been an elevated incidence of contralateral risk reduction mastectomy among individuals diagnosed with BC.[11] In Thailand, the Universal Coverage public health insurance scheme integrated *BRCA* testing for BC patients into its coverage package in 2023. The criteria set forth by Thailand for genetic testing (*BRCA1/2*) in individuals diagnosed with BC are as follows: I. Diagnosis of BC at an age less than 46 years. II. Diagnosis of BC between the ages of 46 and 50 with multiple primary BC. III. Diagnosis of BC at any age with Triple-negative breast cancer (TNBC), male BC, or a family history of breast, ovarian, pancreatic, or prostate cancer among close relatives. The primary individual within this family, referred to as the index case, was diagnosed with DCIS, characterized as a form of noninvasive BC, at the age of 48. The American Society of Breast Surgeons advocates for universal genetic testing benefits for all individuals diagnosed with BC.[5] The NCCN clinical practice guidelines in oncology version 3.2024 define DCIS as non-invasive BC and recommend genetic testing for individuals with a personal history of BC and age younger than 51 years. The American Society of Clinical Oncology (ASCO) recommends that *BRCA1/2* testing be offered to all patients under the age of 66 who are newly diagnosed with stage I-III BC.[12] Germline genetic testing for *BRCA1* and *BRCA2* demonstrates significant cost-effectiveness in benefiting family members within Thailand, a middle-income nation characterized by resource-constrained environments.[13] Conducting multigene panel testing for all women diagnosed with BC proves to be a cost-effective approach.[14]

BRCA1/2 represents a widely recognized gene linked to susceptibility to BC. In addition to *BRCA1/2*, numerous other genes are implicated in BC etiology. According to the database www.omim.org, there are 21 genes identified as having substantial associations with BC. Germline variation is correlated with heightened susceptibility to BC, with variations in specific genes influencing the absolute risk by age 80. For instance, the absolute risk by age 80 associated with various genes is as follows: *BRCA1* (75%), *BRCA2* (76%), *CDH1* (53%), *PALB2* (45%), *CHEK2* (29%), *ATM* (27%), and *NF1* (26%).[15] A germline mutation in *PTEN* significantly elevates the risk of breast cancer in women by approximately 67% to 85% by the age of 70. Consequently, individuals with dense breast tissue are recommended to undergo annual mammograms or breast MRIs starting at the age of 30.[16] A research investigation involving 1,663 BC patients in Brazil revealed that 20.1% of them harbored germline mutations in at least one gene, with 10.1% of the total patient cohort carrying mutations in *BRCA1/2* genes.[17] A cohort study encompassing 480 BC patients of ethnic Chinese descent in Taiwan revealed a 13.5% prevalence of germline mutations. Among these, 61.5% carried mutations in *BRCA1/2* genes, while 39.5% carried mutations in genes other than *BRCA1/2*.[18] A study conducted among 151 BC patients in the southernmost region of Thailand

revealed that 15.2% had germline mutations, with 32% attributable to *BRCA1/2* genes and 68% associated with genes other than *BRCA1/2*.[19]

For individuals identified as *BRCA*-positive carriers within the age range of 25–29 years, the NCCN guideline version 3.2024 recommends annual breast MRI screening. The recommendation is further personalized based on familial history, particularly in cases where a diagnosis of BC occurred before the age of 30. In Thailand, there could be restrictions on the frequency of annual MRI breast examinations. In such cases, the NCCN recommends opting for yearly mammograms as an alternative in instances where MRI screening is unavailable. For individuals aged between 30 and 75 years, the NCCN recommends undergoing both annual mammography and breast MRI screenings. For individuals carrying the *BRCA2* mutation, the European Society for Medical Oncology (ESMO) advises undergoing annual ultrasound examinations, optionally complemented with mammography if MRI breast imaging is inaccessible. This screening protocol typically begins 30 or five years earlier than the age of diagnosis of BC in the youngest affected family member.[20]

In conclusion, we present a non-invasive BC case, underscored by the potential benefits for family members through germline genetic testing. The *BRCA1/2* genetic test offers significant advantages in managing BC patients and their familial relatives.

Funding

This research was supported by Thailand's Fundamental Research Fund of the Fiscal Year 2022 via Prince of Songkla University (Grant no. 172171).

Ethical Declaration

The study protocol was approved by the Human Research Ethics Committee of Naradhiwas Rajanagarindra Hospital (REC 001/2564). The study was conducted according to good clinical practice and the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Conflict of Interest

The authors declare no conflict of interest.

REFERENCES

1. Hodgson A, Turashvili G. Pathology of Hereditary Breast and Ovarian Cancer. Front Oncol. 2020;10:531790. doi: 10.3389/fonc.2020.531790.
2. Lee A, Moon BI, Kim TH. BRCA1/BRCA2 Pathogenic Variant Breast Cancer: Treatment and Prevention Strategies. Ann Lab Med. 2020;40(2):114-21. doi: 10.3343/alm.2020.40.2.114.
3. Ludwig KK, Neuner J, Butler A, et al. Risk reduction and survival benefit of prophylactic surgery in BRCA mutation carriers, a systematic review. Am J Surg. 2016;212(4):660-9. doi: 10.1016/j.amjsurg.2016.06.010.
4. Cortesi L, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. Target Oncol. 2021;16(3):255-82. doi: 10.1007/s11523-021-00796-4.
5. Manahan ER, Kuerer HM, Sebastian M, et al. Consensus Guidelines on Genetic` Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. Ann Surg Oncol. 2019;26(10):3025-31. doi: 10.1245/s10434-019-07549-8.
6. Wendt C, Margolin S. Identifying breast cancer susceptibility genes - a review of the genetic background in familial breast cancer. Acta Oncol. 2019;58(2):135-46. doi: 10.1080/0284186X.2018.1529428.
7. Yoshida R. Hereditary breast and ovarian cancer (HBOC): review of its molecular characteristics, screening, treatment, and prognosis. Breast Cancer. 2021;28(6):1167-80. doi: 10.1007/s12282-020-01148-2.
8. Yoshimura A, Imoto I, Iwata H. Functions of Breast Cancer Predisposition Genes: Implications for Clinical Management. Int J Mol Sci. 2022;23(13):7481. doi: 10.3390/ijms23137481.
9. Kim B, Yun W, Lee ST, et al. Prevalence and clinical implications of germline predisposition gene mutations in patients with acute myeloid leukemia. Sci Rep. 2020;10(1):14297. doi: 10.1038/s41598-020-71386-z.
10. Raphael J, Verma S, Hewitt P, et al. The Impact of Angelina Jolie (AJ)'s Story on Genetic Referral and Testing at an Academic Cancer Centre in Canada. J Genet Couns. 2016;25(6):1309-16. doi: 10.1007/s10897-016-9973-6.
11. Basu NN, Hodson J, Chatterjee S, et al. The Angelina Jolie effect: Contralateral risk-reducing mastectomy trends in patients at increased risk of breast cancer. Sci Rep. 2021;11(1):2847. doi: 10.1038/s41598-021-82654-x.
12. Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi: 10.1200/JCO.23.02225.
13. Lertwilaiwittaya P, Tantai N, Maneeon S, et al. A cost-utility analysis of BRCA1 and BRCA2 testing in high-risk breast cancer patients and family members in Thailand: a cost-effective policy in resource-limited settings. Front Public Health. 2023;11:1257668. doi: 10.3389/fpubh.2023.1257668.
14. Sun L, Brentnall A, Patel S, et al. A Cost-effectiveness Analysis of Multigene Testing for All Patients With Breast Cancer. JAMA Oncol. 2019;5(12):1718-30. doi: 10.1001/jamaoncol.2019.3323.
15. Thorat MA, Balasubramanian R. Breast cancer prevention in high-risk women. Best Pract Res Clin Obstet Gynaecol. 2020;65:18-31. doi: 10.1016/j.bpobgyn.2019.11.006.

16. Ngeow J, Sesock K, Eng C. Breast cancer risk and clinical implications for germline PTEN mutation carriers. Breast Cancer Res Treat. 2017;165(1):1-8. doi: 10.1007/s10549-015-3665-z.
17. Guindalini RSC, Viana DV, Kitajima JPFW, et al. Detection of germline variants in Brazilian breast cancer patients using multigene panel testing. Sci Rep. 2022;12(1):4190. doi: 10.1038/s41598-022-07383-1.
18. Wang YA, Jian JW, Hung CF, et al. Germline breast cancer susceptibility gene mutations and breast cancer outcomes. BMC Cancer. 2018;18(1):315. doi: 10.1186/s12885-018-4229-5.
19. Sukpan P, Sangkhathat S, Sriplung H, et al. Exome Sequencing Reveals Novel Germline Variants in Breast Cancer Patients in the Southernmost Region of Thailand. J Pers Med. 2023;13(11):1587. doi: 10.3390/jpm13111587.
20. Sessa C, Balmaña J, Bober SL, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1):33-47. doi: 10.1016/j.annonc.2022.10.004.