From Variant to Vigilance: Clinical Implications of *CHEK2* Mutation-Associated Breast Cancer and Second Malignancies in a Non-Western Cohort

Hikmat Abdel-Razeq, MD[1,2]; Hira Bani Hani, MS.c[1]; Faris Tamimi, MD [1]; Lulwa Al-Saket, MS.c[1]; Sarah Abdel-Razeq, MD[2]; Baha Sharaf, MD[1]; Hala Abu-Jaish, MD[1]; Yazan Talab, MD[1]; Areej Al-Atari, RN[1]; Maryam El-Atrash, MD[1]; Tamer Al-Batsh, MD[1]; Malek Horani, MD[1]; Laith Barakat, MD[1]; Yosra Al Masri, MD[1]; Osama El Khatib, MD[1]

[1]King Hussein Cancer Center, [2]School of Medicine, University of Jordan

Abstract

Background: *CHEK2* is a moderate-penetrance DNA-repair gene associated with increased risk of ER-positive breast cancer and other malignancies.
Methods: Retrospective study for breast cancer patients with P/LP *CHEK2* mutation.
Results: We analyzed 59 female carriers at King Hussein Cancer Center (median age 48). All tumors were ER-positive, mostly low to intermediate grade. The c.592+3A>T splice-site variant predominated (39%), suggesting a possible founder effect in the Arab population. 27% developed second primary malignancies, emphasizing the need for extended surveillance.
Conclusion: With an estimated regional prevalence of 7.3%, the highest reported globally, this study highlights the unique mutation spectrum among Jordanians and supports implementing region-specific databases, comprehensive multigene testing, and family-centered preventive programs to optimize hereditary-cancer management in the Middle East.

Introduction

- The *CHEK2* (Checkpoint Kinase 2) gene, located on chromosome 22q12.1, encodes a serine/threonine kinase that plays a pivotal role in the DNA-damage checkpoint, cell-cycle control, and apoptosis.[1,2]
- Pathogenic or likely pathogenic (P/LP) *CHEK2* variants confer a moderate (2–3-fold) increase in breast-cancer risk, particularly ER-positive subtypes, and have been associated with colorectal, thyroid, prostate, and other malignancies. [3,4]
- Although *BRCA1/2* mutations dominate hereditary cancer discussions, moderate-penetrance genes such as *CHEK2* remain under-recognised, despite being the third most frequent gene identified on multigene panels.[2]
- Global prevalence varies:
  - Up to 5 % in Northern/Eastern Europe
  - 2–3 % in Central Europe
  - 1–2 % in North America
  - < 1 % in Asia and Africa
- However, Middle Eastern data reveal an unexpectedly high prevalence (6.8–7.3 %), the highest worldwide.

KHCC is the only reporting centre for *CHEK2* in the Middle East, and this cohort represents both the largest *CHEK2* study and the first detailed regional clinical-genetic correlation, addressing a major data gap.

Methods and Materials

- A retrospective study of breast cancer patients with germline P/LP *CHEK2* mutations identified through multigene panel testing (20-gene or 84-gene panels).
- Testing was done at one of two accredited international reference genomic labs (Invitae and Agiomix).
- Clinical variables included:
  - Demographics, tumor histology and grade, hormone receptor status, treatment modalities.
  - Family history of malignancy.
  - Presence of second primary cancers and findings from screening colonoscopies.
  - *CHEK2* variant type and co-occurrence with other germline P/LP mutations.

All data were reviewed and validated through the King Hussein Cancer Center hereditary cancer registry.

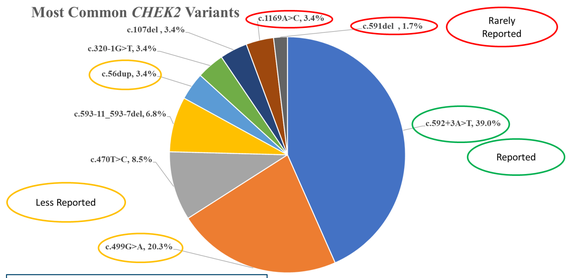
Table 1. Patient Characteristics.

Characteristics		Number (%)
Age at diagnosis	Median (Range)	48 (28-77)
	≤ 50	**35 (59.3)**
	> 50	24 (40.7)
Gender	**Female**	**59 (100)**
Histology	**IDC**	**48 (81.4)**
	ILC	8 (13.6)
	DCIS	2 (3.4)
IHC	**ER Positive**	**59 (100)**
	PR Positive	50 (86.2)
	Her-2 Positive	13 (23.2)
Neoadjuvant	**Yes**	**25 (43.1)**
Surgery	Breast-Conserving Surgery	16 (27.1)
	Mastectomy	**31 (52.5)**
Family History of Cancer	**Positive**	**54 (91.5)**
	Negative	5 (8.5)
Family History of Breast Cancer (n= 54)	**Positive**	**44 (81.5)**

Results

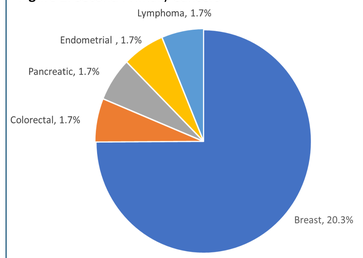
- A total of 59 female breast cancer patients with germline CHEK2 variants
- Median age: 48 years (range 28–77); 59.3 % diagnosed ≤ 50 years.
- Tumor type: Invasive ductal carcinoma (81.4 %) predominated.
- Receptor status: All tumors ER positive.
- Treatment: 48 % received neoadjuvant therapy; 52.5 % underwent mastectomy.
- Family history: 91.5 % had a positive cancer history (81.5 % breast cancer in relatives).
- The c.592+3A>T splice-site variant was the most frequent (39 %). Rarely reported variants: *c.1169A>C (p.Tyr390Ser)* and *c.591del (p.Val198Phefs7).* (Figure 1)

Figure 1. *CHEK2* Variant



- Second primary cancers were identified in 16 (27.1%) patients and mostly were breast cancer (n=12, 20.3%) and one case each of colorectal, endometrial, pancreatic and lymphoma. (Figure 2)
- Among those who underwent screening colonoscopy (n=25), 3 patients (12.0%) were diagnosed with colorectal cancer, and 3 others (12.0%) had tubular adenomas and hyperplastic polyps.

Figure 2. Second Primary Cancers



Discussion

- *CHEK2*-associated breast cancer in this non-Western cohort mirrors global patterns, predominantly ER-positive, yet reveals distinct regional molecular features.
- The *c.592+3A>T* splice-site variant was the most frequent mutation (≈39 %), indicating a strong founder effect in Jordan and neighboring Arab populations.
- The *CHEK2* mutation prevalence (7.3 %) observed at King Hussein Cancer Center is the highest reported worldwide, establishing Jordan as a regional reference for *CHEK2-related* genetic epidemiology.
- Several rare or previously under-reported variants were also detected, including: (Figure 1) [5,6]
  - *c.1169A>C (p.Tyr390Ser)*
  - *c.591del (p.Val198Phefs7)*
  - *c.56dup (p.Gln20Thrfs57)*
  - *c.470T>C (p.Ile157Thr)*
- These unique alterations highlight regional genetic diversity and reinforce the need for population-specific variant classification and interpretation.
- Cascade-testing programs at KHCC have been highly effective in identifying carrier families, leading to early detection of breast and colorectal cancers among relatives through targeted screening, demonstrating the clinical utility of family-based genetic testing.
- The identification of co-mutations in *APC, BRCA2, PALB2,* and *RAD51D* further supports the use of broad multigene panels over limited *BRCA-only* testing.
- Collectively, these results underscore the importance of developing region-specific variant databases, tailored surveillance guidelines, and national cascade-testing frameworks to advance precision oncology and hereditary cancer prevention across the Middle East.

Conclusions

This study provides insight into the clinical and molecular landscape of *CHEK2-positive* breast cancer patients in a non-Western cohort.

- *CHEK2* mutation prevalence in Jordan (6.8–7.3 %) is the highest worldwide, with a unique variant spectrum dominated by *c.592+3A>T.*
- Second primary malignancies (27 %) and multigene co-mutations highlight the need for lifelong, multi-organ surveillance.
- Cascade testing programs at KHCC demonstrate tangible benefits in early detection and risk reduction among families.
- This cohort fills a major data gap and sets a regional benchmark for integrating *CHEK2* testing into routine oncogenetic care in the Middle East.

Contact

Hikmat Abdel-Razeq, MD
King Hussein Cancer Centre
Email: habdelrazeq@KHCC.JO
Tel: +962 6 5300460, Ext: 1000
Mobile: + 962 79 643 3993

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PS3-05-04

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