CHEK2-associated multiple primary malignancies: a case report with longitudinal multidisciplinary management

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ABSTRACT

Background: Germline CHEK2 mutations confer a significant risk of developing multiple malignancies, often at an earlier age than the general population. While less widely recognized than BRCA1/2, CHEK2 is increasingly clinically relevant and requires tailored surveillance and multidisciplinary management.

Case Presentation: We report a 57-year-old man from Northern Portugal, a carrier of a germline CHEK2 mutation, who developed three primary malignancies over a decade: renal cell carcinoma, rectal adenocarcinoma, and papillary thyroid carcinoma. His family history revealed clustering of cancers, including breast, prostate, laryngeal, brain, and sarcoma, with a paternal aunt confirmed as a CHEK2 carrier. Care was organized longitudinally, with primary care playing a central role in coordinating follow-up across oncology, genetics, endocrinology and hematology.

Conclusion: This case emphasizes the complexity of managing multiple primary malignancies in CHEK2 carriers and underscores the value of organized multidisciplinary care and risk-adapted investigation.

Keywords: CHEK2, hereditary cancer, genetic variant, multiple malignancies, family medicine.

Type of Article: CASE REPORT **Specialty:** Family Medicine

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Background

The CHEK2 gene, discovered in 1998, encodes the CHK2 protein, a key tumor suppressor involved in the cellular response to DNA damage. Upon detection of double-strand breaks or other genomic instability, CHK2 is activated and functions to pause the cell cycle, allowing DNA repair primarily via homologous recombination (HRR), or to initiate programmed cell death (apoptosis) if the damage is irreparable [1,2].

The initial correlation between CHEK2 mutations and an elevated cancer susceptibility was observed when rare germline variants of this gene were identified in families exhibiting characteristics analogous to those of Li-Fraumeni syndrome (LFS) [3], a rare hereditary autosomal dominant disorder that is characterized by a wide range of malignancies that appear at an unusually early age [4], and are associated with p53 gene [5].

LFS is typified by early-onset, diverse malignancies, particularly breast cancers and sarcomas during childhood. The presence of a wild-type p53 gene in some individuals supported the hypothesis that CHEK2 germline mutations may act as an alternative genetic mechanism underlying cancer risk in LFS-like cases [3,4].

The relationship between CHEK2 mutations and other malignancies remains inconclusive or inconsistent across studies. Importantly, the cancer risk associated with CHEK2 pathogenic variants may be influenced by modifying factors, including personal and familial cancer history, leading to variability in clinical expression [6].

Providing genetic and psychological counselling to individuals carrying pathogenic or likely pathogenic variants in the CHEK2 gene is an important component of cancer risk management [7]. Counselling should include evidence-based recommendations on preventive measures, personalized surveillance protocols, and appropriate follow-up [7]. Improving patients' health literacy in this context is essential to promote informed decision-making, early detection, and risk reduction. The family doctor is often the first point of contact in the healthcare system and plays a central role in identifying patients at risk [8]. It is therefore vital that, when a CHEK2-related predisposition is suspected, the family physician ensures timely

referral to relevant specialties, such as medical genetics and oncology, to facilitate early diagnosis, initiate appropriate care, and minimize long-term morbidity [9] .

We report the case of a male CHEK2 carrier with multiple primary malignancies diagnosed over more than a decade, emphasizing not only the clinical management tasks but also the importance of coordinated care and psychosocial resilience. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Case Presentation

A 57-year-old man from Northern Portugal, divorced and father of two sons (aged 17 and 29 years), presented with multiple primary malignancies and a notable family history of cancer. He has a significant smoking history, estimated at 67.5 pack-years (1.5 packs per day for 45 years). Previously, the patient had been attending multiple hospital specialists without coordinated follow-up. Upon referral to the Family Health Unit, the team ensured coordinated follow-up of his chronic conditions, optimized his medication regimen, and improved his functional health literacy in accordance with his clinical needs.

Family history

The patient presented a notable familial oncologic burden. His father was diagnosed with laryngeal carcinoma and died at the age of 68 years. His mother, currently 77 years old, has no documented history of malignancy. A paternal aunt developed bilateral invasive breast carcinoma at the age of 55 years and was confirmed to be a carrier of a likely pathogenic CHEK2 germline variant c.904G>A (p.Glu302Lys). Among his siblings, one brother was diagnosed with a brain tumor at 47 years, prostate cancer at 52 years, and sarcoma at 53 years, and subsequently died. The remaining two brothers are alive, without a cancer history, and declined genetic testing. His sons are apparently unaffected, with no known history of cancer until now.

A genogram illustrating this family history is shown in Figure 1. The data were collected on August 1st, 2025.

The patient's personal oncological trajectory began in 2013 (age 46) with a diagnosis of clear cell renal carcinoma, classified as pT1b and Fuhrman grade II. He underwent partial nephrectomy with preservation of renal function, and no recurrence was identified during subsequent follow-up imaging.

In 2020 (age 51), he underwent surgery for a rectal adenocarcinoma, with no requirement for adjuvant chemotherapy or radiotherapy. Later the same year, he was diagnosed with papillary thyroid carcinoma, treated with total thyroidectomy, followed by routine postoperative surveillance. Postoperative cervical scintigraphy demonstrated focal tracer uptake in the thyroid bed, consistent with expected postoperative activity (Figure 2).

In March 2025, follow-up laboratory tests revealed markedly elevated thyroid-stimulating hormone levels (75.76 µIU/ml) with a serum thyroglobulin level of 6.71 ng/ml and negative anti-thyroglobulin antibodies. Cervical ultrasound showed no evidence of residual thyroid tissue or suspicious lymphadenopathy. These findings were interpreted as an indeterminate response, with the elevated TSH reflecting insufficient levothyroxine replacement at that time. A target TSH range of 0.1 to 0.5 µIU/ml was defined, and dose adjustment was planned, recognizing the impact of TSH levels on thyroglobulin interpretation and recurrence risk assessment.

In January 2023, during routine follow-up for type 2 diabetes mellitus, laboratory testing revealed persistent erythrocytosis, with hemoglobin levels ranging from 19 to 20 g/dL and hematocrit values ranging from 55% to 58%. Previous analyses showed mildly elevated hemoglobin levels dating back to at least 2008.

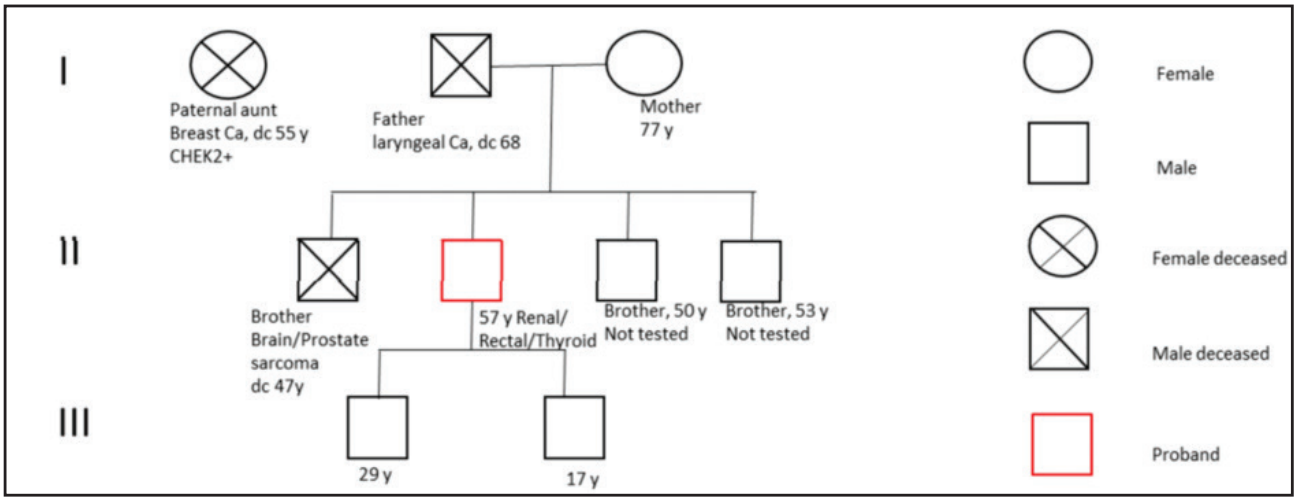

Figure 1. *Pedigree of the patient's family history (CHEK2-related cancer).*

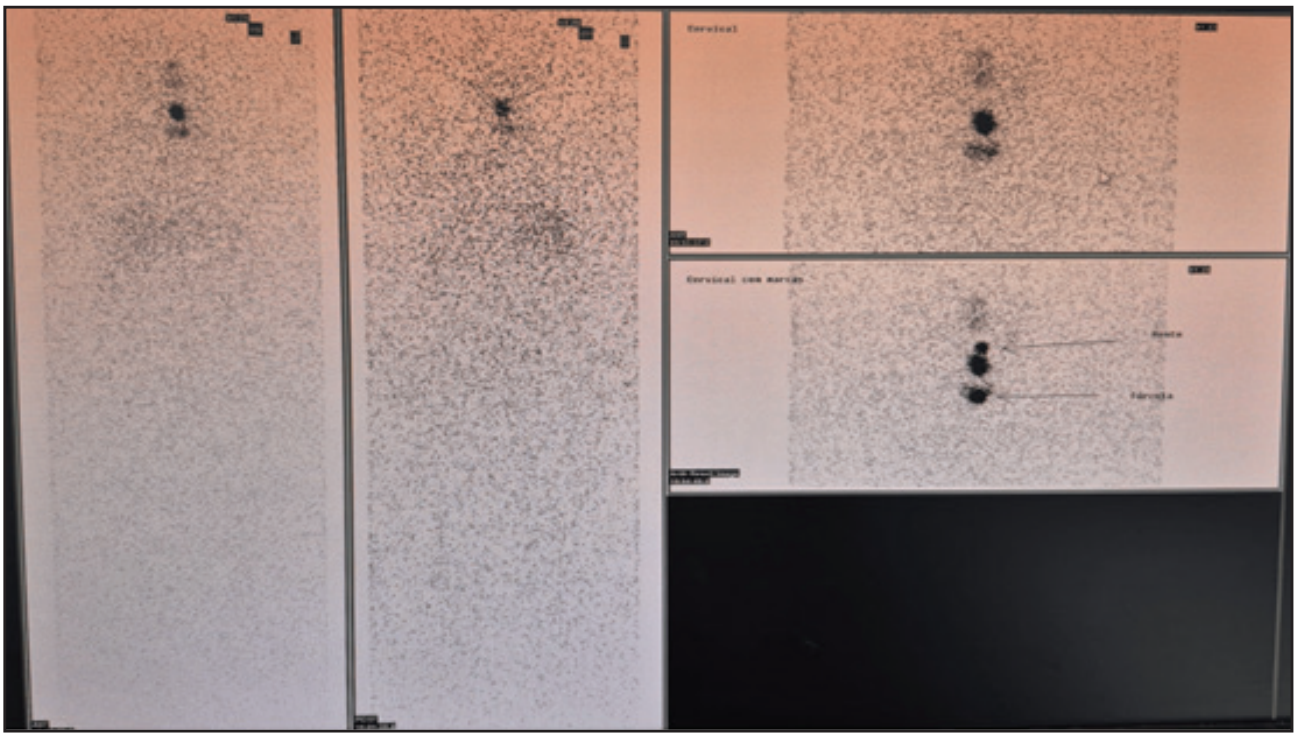

Figure 2. *Body scintigraphy after therapy: Foci of radionuclide uptake were detected in the anterior cervical projection, consistent with residual functioning thyroid. The remaining biodistribution of the radionuclide shows no significant changes.*

A structured hematological evaluation revealed suppressed serum erythropoietin levels (<1), negative JAK2 V617F and exon 12 mutations, and a norm cellular bone marrow with relative erythroid hyperplasia, without features of a myeloproliferative neoplasm; imaging and pulmonary function tests showed no secondary causes. In the absence of a primary hematological disorder and given the patient's long-standing tobacco exposure, the findings were considered most consistent with secondary polycythemia, possibly aggravated by chronic smoking.

Genetic Evaluation

Given the clustering of malignancies in the patient and his family, genetic evaluation was performed. Germline testing identified a heterozygous CHEK2 variant, c.904G>A (p.Glu302Lys), shared with his paternal aunt. Initially classified as a variant of uncertain significance, it was reclassified as likely pathogenic in November 2024 based on segregation data and accumulating evidence. The patient was informed, referred for genetic counselling, and cascade testing was offered to first-degree relatives.

Current clinical evaluation

The patient has two sons (29 and 17 years old), both currently unaffected. At the time of evaluation, the patient appeared anxious but maintained a confident and future-oriented perspective, reporting particular concern regarding the potential implications of his genetic condition for his sons. On objective examination, he was alert and oriented, well hydrated, anicteric, and eupnoeic. His weight was 82 kg and height 1.74 m. No palpable peripheral lymphadenopathies were detected, and breast examination revealed no nodules. There was no peripheral edema.

Post-thyroidectomy laboratory assessment demonstrated markedly elevated thyroid-stimulating hormone (TSH) levels at 75.76 µIU/ml (reference range: 0.4-4.0 µIU/ml), with serum thyroglobulin measured at 6.71 ng/ml (reference range: 1.4-78.0 ng/ml) and anti-thyroglobulin antibodies at 0.9 IU/ml (reference < 4.0 IU/ml). Thyroid ultrasound revealed no residual thyroid tissue and identified a single benign-appearing lymph node at level V, measuring 17 × 6 mm, without suspicious morphological features.

Previous hematological investigations confirmed a negative Janus kinase 2 (JAK2) mutation, and a bone marrow biopsy was reported as normal, with no evidence of a myeloproliferative neoplasm. His regular medication included pantoprazole 20 mg daily, acetylsalicylic acid 100 mg daily, levothyroxine 0.125 mg daily, dapagliflozin 10 mg daily, and metformin 1000 mg daily. No known allergies. Figure 3 shows a timeline of events.

Risk Management and Follow-up

A coordinated surveillance and risk-reduction strategy was established in collaboration with multiple specialties. From an oncological perspective, annual prostate-specific antigen (PSA) testing was recommended, given the patient's increased estimated lifetime risk of prostate cancer associated with CHEK2 mutations. Colorectal

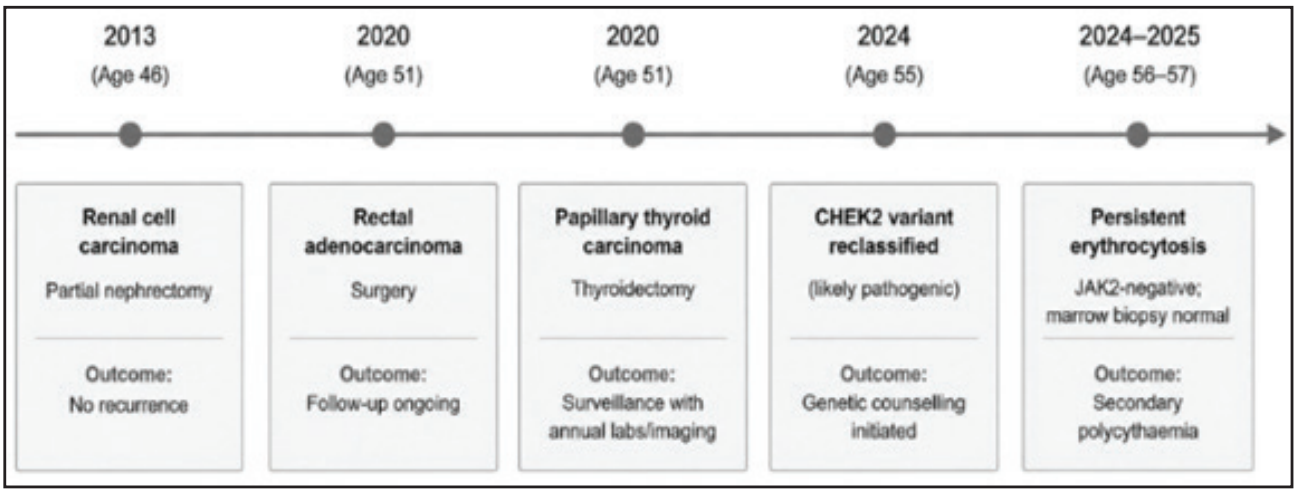

Figure 3. *Timeline of events.*

surveillance was maintained at the Portuguese Institute of Oncology in Porto, Portugal, and the patient was counselled on awareness of male breast changes, including the potential for atypical presentations.

The subsequent endocrinology follow-up is centered on the continuous monitoring of thyroid function and the presence of recurrence markers. This is accompanied by periodic reassessment of thyroid-stimulating hormone, thyroglobulin, and anti-thyroglobulin antibodies, in addition to interval cervical ultrasound. In primary care, the emphasis was on lifestyle counselling, including smoking cessation, dietary patterns, physical activity, weight optimization, and stress reduction. Standard cardiovascular risk-prevention measures were reinforced, and education on male-specific breast self-examination was provided.

The patient was also referred to psycho-oncology services to support adaptive coping strategies and resilience throughout long-term cancer survivorship. In addition, he was enrolled in the ICF Genturis Network research program to improve structured surveillance in hereditary cancer predisposition syndromes.

Discussion

This case underscores the essential role of the family doctor in recognizing disease patterns, identifying hereditary cancer syndromes, and ensuring timely referral and coordinated long-term follow-up. It also illustrates the clinical complexity of CHEK2 carriers, who may develop multiple primary malignancies and require lifelong surveillance, often presenting cancers earlier and across several organ systems [4,5].

Although CHEK2 variants are well-established in breast and prostate cancer predisposition, their association with other malignancies such as renal cell carcinoma, colorectal cancer, and thyroid cancer remains less consistent across studies [4]. In this case, the coexistence of multiple primary malignancies may reflect a combination of genetic susceptibility, environmental factors such as tobacco exposure, and stochastic processes, rather than a direct causal relationship between tumor types [1].

Modification of lifestyle factors is critical in overall risk reduction [10]. In this patient, long-standing tobacco use may have contributed both to his multiple cancers and to the persistence of erythrocytosis, despite exclusion of primary hematological disease. His resistance to smoking cessation represents an ongoing challenge requiring motivational interviewing and multidisciplinary support.

Family physicians play a pivotal role in coordinating care, supporting informed decision-making, and ensuring continuity across the patient's diagnostic and surveillance pathway and facilitating cascade testing of at-risk relatives [8,11].

The integration of genetic risk assessment into primary care can be further guided by national clinical tools, such as the Portuguese Therapeutic Guidance Manual for Hereditary Cancer (2018) from the Portuguese Institute of Oncology (IPO), Porto, Portugal [12]. This guide recommends considering hereditary cancer syndromes in individuals with features such as two or more close relatives affected by the same type of malignancy; a history of cancer across multiple generations; early-onset cancer diagnoses; multiple primary tumors in the same individual; unusual combinations of neoplasms within a family; or the presence of a known hereditary syndrome.

Patient Perspective

The patient has faced significant psychosocial stressors, including employment loss, financial insecurity, and prolonged medical follow-up across multiple specialties. Despite these challenges, he consistently demonstrated optimism, engagement with care, and trust in his medical team. He described himself as "the patient with the most serious illnesses but the least problematic," a remark reflecting his pragmatic approach rather than denial or minimization of risk.

Psychological adaptability was explored using the Brief Resilience Scale (BRS) [13], yielding a score of 4.0/5.0. Based on validation studies, this value falls within the range typically associated with normal resilience in adult populations. This result should be recognized as descriptive within the context of a single case report.

Conclusion

In family medicine, the ability to recognize early warning signs, understand the patient's illness experience, and navigate diagnostic uncertainty is important. In this situation, the family doctor's core competencies, such as person-centered care, longitudinal follow-up, and comprehensive assessment of both disease and illness, were decisive for ensuring timely referral, appropriate surveillance, and meaningful support throughout the patient's journey. The identification of a CHEK2 mutation enabled risk-adapted screening, multidisciplinary management, and cascade testing within the family.

Acknowledging the psychosocial impact of hereditary cancer is equally important, as many patients face fear, uncertainty, and difficulty implementing lifestyle changes. A collaborative approach between oncology, endocrinology, hematology, psycho-oncology, and primary care promotes effective risk reduction and sustained continuity of care.

What is new?

Family physicians should maintain a high index of suspicion for hereditary cancer syndromes when two or more family members are affected by cancer, particularly at younger ages, ensuring timely referral for genetic evaluation. They also play a key role in coordinating long-term, holistic care, bridging genetic diagnosis with family risk assessment while maintaining comprehensive management of the patient.

List of Abbreviations

BRS	Brief Resilience Scale
CHEK2	Checkpoint Kinase 2
CHK2	Checkpoint Kinase 2 protein
DNA	Deoxyribonucleic Acid
HRR	Homologous Recombination Repair
IPO	Portuguese Institute of Oncology
JAK2	Janus Kinase 2
LFS	Li-
PSA	Prostate-Specific Antige
TSH	Thyroid-Stimulating Hormone
VUS	Variant of Uncertain Significance

Conflict of interests

The authors declare that there is no conflict of interest regarding the publication of this article.

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Consent for publication

Written informed consent was obtained from the patient.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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382 **Summary of the case**

1	Patient (gender, age)	57 years old, male
2	Final diagnosis	Multiple malignant tumors
3	Symptoms	none
4	Medications	Symptomatic treatment given
5	Clinical procedure	Surgery
6	Specialty	Oncology/family medicine