CDC73 (Hyperparathyroidism-jaw tumour syndrome) – risk management

ID: 3575 v.6 **Under review**

In this document the terms 'male' and 'female' refer to sex assigned at birth. For more information about providing individualised care refer to Resources to assist in the care of transgender individuals referred to a clinical genetics service or familial cancer centre

Related pages:

- Informing family members about hereditary cancer
- CDC73 – genetic testing
- Facts for people and families with Hyperparathyroidism-jaw tumour (HPT-JT) syndrome

Summary

Hyperparathyroidism-jaw tumour syndrome (HPT-JT) is an autosomal dominant syndrome characterised by primary hyperparathyroidism (PHPT) secondary to parathyroid neoplasm and ossifying fibromas/cemento-ossifying fibromas of the maxilla or mandible.

The care of an individual who has developed a related tumour or cancer should be individualised based on their clinical situation, their family history and the monitoring they need as part of their treatment and post-treatment follow-up.

The risk management of an individual with a pathogenic variant in two or more genes that confer a predisposition to cancer should also be individualised.

Target group

- Unaffected known or obligate CDC73 gene pathogenic variant carrier
- Individuals at 50% risk of inheriting a CDC73 gene pathogenic variant

Exclusion criteria

- A CDC73 gene pathogenic variant carrier already diagnosed with a relevant cancer/tumour
- Individual with a variant of uncertain significance

Lifetime risk of cancer/tumour

Cancer/tumour type	Risk for this group	General population risk by age 85 years*
Parathyroid carcinoma	Up to 23% lifetime risk[1]	Rare

**Cancer Institute NSW (CINSW) 2019. Cancer Statistics NSW: Parathyroid Cancer Incidence Risk by age 85 years (2014 data).*

Malignant uterine tumours have been reported but appear to be rare and routine screening is not recommended. See comment on malignant uterine tumours in the evidence section below.

Lifetime risk of non-cancer manifestations

Tumour type	Risk for this group	General population risk by age 85 years
Hyperparathyroidism (includes parathyroid carcinoma)	75-100% by age 70 years[1, 2]	Unable to obtain
Ossifying fibroma/ cemento-ossifying fibroma of the maxilla or mandible	28.4% by age 40 years[1]	Unable to obtain
Renal lesions (hamartomas, cysts and more rarely malignant tumours e.g. adult Wilms tumour and papillary renal cell carcinoma)	15.6% lifetime risk[1]	Unable to obtain

Cancer/tumour risk management guidelines

The choice of risk management strategy should take into account current age, other health issues and age-related cancer risk. Risks and benefits of interventions should be discussed with an experienced medical professional.

The impact of lifestyle on cancer risk should be discussed e.g. exercise most days for at least 30 minutes at moderate or strenuous intensity, maintain a healthy weight, have a healthy diet, limit alcohol intake, do not smoke and avoid excessive sun exposure.

Cancer/tumour type	Recommendations		
Parathyroid adenoma and/or carcinoma	**Surgical**	Prophylactic surgery not indicated	
	Surveillance	**Age**	**Strategy and frequency**
		From age 10 years	Annual fasting calcium, phosphate, vitamin D and parathyroid hormone Annual clinical examination of the neck

Non-cancer risk management guidelines

Tumour type	Recommendations		
		Age	**Strategy and frequency**
Ossifying fibroma of the maxilla or mandible	**Surveillance**	From age 10 years	5-yearly orthopantogram (OPG) with neck shielding
Renal complications	**Surveillance**	From age 10 years	5-yearly renal ultrasound. If renal cysts detected, monitor renal function annually
Benign uterine tumours (e.g. leiomyomas)	**Surveillance**	There is no evidence to support routine surveillance for uterine tumours. If symptomatic and clinically indicated, further investigation with pelvic ultrasound, and further imaging studies if needed.	

Management of associated health issues

Pregnancy

If a woman with a CDC73 gene pathogenic variant develops hypercalcaemia during pregnancy, referral to a specialist high risk pregnancy unit should be considered.

Evidence for risk management guidelines

Parathyroid neoplasms

Surgical

Compared to individuals with sporadic PHPT, individuals with a CDC73 gene pathogenic variant have an increased risk of the following:

- larger parathyroid tumours which demonstrate distinctive morphological features
- synchronous or metachronous multiglandular disease
- local or distant recurrence
- postoperative hungry bones syndrome.

These factors should be considered when planning the surgical and post-surgical management of individuals with a CDC73 gene pathogenic variant and PHPT.

Biopsy of suspicious neck lesions in these patients is discouraged due to risk of seeding parathyroid cancer cells, the difficulty it creates in interpreting the pathology of excision specimen and the limited information it provides.[3] If there is a suspicion of parathyroid carcinoma (i.e. large tumour on imaging, palpable neck mass, clinical and biochemical evidence of severe hypercalcaemia) then “en bloc” resection is recommended of the affected gland, surrounding tissues, ipsilateral thyroid lobe, ipsilateral normal parathyroid and thymus. This is to reduce the risk of capsular spillage, local seeding and potential need for reoperation on the same side.[4]

Rare cases of non-functioning parathyroid carcinoma have been reported in individuals with a CDC73 gene pathogenic variant. Some authors recommend consideration of periodic neck ultrasound in addition to biochemical screening. However, the age of commencement and optimal interval of imaging has not been defined.

Surveillance

The youngest age of PHPT in HPT-JT is reported to be 7 years, while the youngest age of parathyroid carcinoma is reported to be 15 years.[3]

There is emerging evidence that CDC73 germline variants that disrupt the C-terminal domain are associated with an increased risk of parathyroid carcinoma.[5] These patients may benefit from closer monitoring for parathyroid carcinoma.

Ossifying fibroma/cemento-ossifying fibroma of the maxilla or mandible

There is currently insufficient available data to indicate whether there is an age at which jaw imaging can be ceased in individuals who have had serial normal imaging.

Uterine tumours

The lifetime risk of developing uterine tumours in females with a CDC73 pathogenic variant is approximately 45%.[4] The incidence of uterine leiomyomas in females with a CDC73 pathogenic variant is similar to that of the general population.[6]

While malignant uterine tumours have been reported in females with a CDC73 pathogenic variant, they appear to be rare. There is no evidence to support routine surveillance for uterine tumours. Females with a CDC73 pathogenic variant should be aware of the risk of uterine tumours and report any new symptoms to their General Practitioner. Menorrhagia and infertility have been reported in females with CDC73 pathogenic variants and may potentially indicate a uterine tumour. Further investigation should be undertaken if clinically indicated with pelvic ultrasound and then further imaging studies if needed.[4]

Renal lesions

Wilms tumours have been reported in a small number of patients with CDC73 pathogenic variants from the age of 8 years. There is insufficient evidence to estimate the risk of Wilms tumour in the setting of a CDC73 pathogenic variant, but it is likely to be <1%, and the intensive surveillance that would be recommended in other conditions associated with Wilms tumours is not recommended. The current recommendation for 5-yearly ultrasound is predominantly to assess for renal cysts.[2, 7]

Support and information

First degree blood relatives (parents/brothers/sisters/children) are at up to 50% risk of having inherited the pathogenic variant . More distant relatives may also be at risk of inheriting the pathogenic variant. Genetic relatives should be referred to a clinical genetics service or familial cancer centre to discuss predictive genetic testing.

Informing family members about hereditary cancer

Website resources

Centre for Genetics Education - NSW Health

Genetic Alliance Australia

References

1 Torresan, F. and M. Iacobone 2019. "Clinical Features, Treatment, and Surveillance of Hyperparathyroidism-Jaw Tumor Syndrome: An Up-to-Date and Review of the Literature." Int J Endocrinol 2019: 1761030.

2 van der Tuin, K., C.M.J. Tops, M.A. Adank, et al. 2017. "CDC73-related disorders: clinical manifestations and case detection in primary hyperparathyroidism." J Clin Endocrinol Metab 102(12): 4534-4540

3 Gill, A. J., G. Lim, V.K.Y. Cheung, et al. 2019. "Parafibromin-deficient (HPT-JT type, CDC73 mutated) parathyroid tumors demonstrate distinctive morphologic features." Am J Surg Pathol 43(1): 35-46.

4 Iacobone, M., V. Camozzi, C. Mian, et al. 2020. "Long-term outcomes of parathyroidectomy in hyperparathyroidism-jaw tumor syndrome: Analysis of five families with CDC73 mutations." World Journal of Surgery 44(2): 508-516.

5 Li, Y., J. Zhang, P. R. Adikaram, et al. 2020. "Genotype of CDC73 germline mutation determines risk of parathyroid cancer." Endocr Relat Cancer 27(9): 483-494.

6 Kaganov, H. and A. Ades 2016. "Uterine fibroids: Investigation and current management trends." Aust Fam Physician 45(10): 722-725.

7 Mahamdallie, S., S. Yost, E. Poyastro-Pearson, et al. 2019. "Identification of new Wilms tumour predisposition genes: an exome sequencing study." Lancet Child Adolesc Health 3(5):322-331.

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Wasserman, J. D., et al. 2017. "Multiple Endocrine Neoplasia and Hyperparathyroid-Jaw Tumor Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood." Clin Cancer Res 23(13): e123-e132.

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History

Version 6

Date	Summary of changes
15/09/2023	New eviQ cancer genetics risk management template changes applied - PDF of changes. Version number changed to V.6.

Version 5

Date	Summary of changes
13/02/2023	The following sections of the document were updated to align with the new eviQ cancer genetics risk management template: • Summary: ◦ Template sentence updated. • Target population: ◦ Added to exclusion criteria "Individual with a variant of uncertain significance". • Cancer/tumour risk management guidelines: ◦ Template sentence updated. ◦ Lifestyle factors sentence moved above table. • Management of associated health problems: ◦ Accordion title changed to "Management of associated health issues". Version number increased to V.5.

Version 4

Date	Summary of changes
14/11/2021	Protocol discussed at September 2021 cancer genetics reference committee meeting. Discussions continued via MS Teams. Approved for publication with the following changes made: • Summary: minor wording changes • Lifetime risk of cancer/tumour: ◦ Lifetime risk of parathyroid carcinoma: 'Up to 38%' changed to 'Up to 23%' and new reference added ◦ New paragraph added below table: 'Malignant uterine tumours have been reported but appear to be rare and routine screening is not recommended. See comment on malignant uterine tumours in the evidence section below.' • Lifetime risk of non-cancer manifestations: ◦ Hyperparathyroidism risk: '75% by age 70 years' changed to '75-100% by age 70 years' and new reference added ◦ Ossifying fibroma/cemento-ossifying fibroma risk: 'Up to 30% by age 40 years' changed to '28.4% by age 40 years' and new reference added ◦ Renal lesions risk: 'Up to 13% lifetime risk' changed to '15.6% lifetime risk' and new reference added • Cancer/tumour risk management guidelines: 'Annual clinical examination of the neck' added to Strategy and frequency • Non-cancer risk management guidelines: new row added to table 'Benign uterine tumours (e.g. leiomyomas)' • Evidence for risk management guidelines: ◦ Parathyroid neoplasms: reviewed and updated ◦ Uterine tumours: reviewed and updated ◦ Renal lesions: added. Version increased to V.5. Review in 2 years.

Version 3

Date	Summary of changes
20/12/2019	"Mutation" changed to "pathogenic variant" throughout document for consistency among eviQ cancer genetics protocols per agreement among the cancer genetics reference committees' chairs. Definition of "pathogenic variant" added as a pop-up. Version number increased to V.3.
18/12/2020	The following sections of the protocol were updated to align with the revised eviQ cancer genetics risk management template: • Lifetime risk of cancer: heading changed to "Lifetime risk of cancer/tumour" • Cancer risk management guidelines: ◦ Heading changed to "Cancer/tumour risk management guidelines" ◦ Sentence added above table "The choice of risk management strategy should take into account current age, other health issues and residual cancer risk" ◦ Surveillance: "Age to begin" changed to "Age"

Date	Summary of changes
	• Support and information: template wording updated.

Version 2

Date	Summary of changes
28/08/2019	Protocol title changed from 'Risk management for hyperparathyroidism-jaw tumour (HPT-JT) syndrome' to 'CDC73 (Hyperparathyroidism-jaw tumour syndrome) – risk management' in accordance with Cancer Genetics Reference Committees' consensus. Version number increased to V.2.

Version 1

Date	Summary of changes
19/03/2019	New protocol developed and presented at Nov 2018 RCM. Discussion continued over email and approved for publication. Version V.1. Review second yearly.

First approved: 19 March 2019
Last reviewed: 14 November 2021
Review due: 14 November 2023