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ORIGINAL ARTICLE

Thyroid nodules in xeroderma pigmentosum patients: a feature of premature aging

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Abstract

Purpose Xeroderma pigmentosum (XP) is an autosomal recessive disease with defective DNA repair, a markedly increased risk of skin cancer, and premature aging. Reports from North Africa have described thyroid nodules in XP patients, but thyroid nodule prevalence has never been determined in XP patients enrolled in our natural history study at the National Institutes of Health (NIH).

Methods We performed thyroid ultrasound examinations on all 29 XP patients examined from 2011 to 2019 and assessed nodule malignancy using the Thyroid Imaging Reporting and Data System. Thyroid nodule prevalence was also obtained from comparison cohorts. DNA sequencing was performed on thyroid tissue from XP patients who had surgery for thyroid cancer.

Results Thyroid nodules were identified in 18/29 XP patients (62%). The median age of patients with thyroid nodules in our XP cohort (20 years) was younger than that of three comparison groups: 36 years (California study—208 subjects), 48 years (Korean study—24,757 subjects), and 52 years (NIH—682 research subjects). Multiple (2–4) thyroid nodules were found in 12/18 (67%) of the patients with nodules. Autopsy examination revealed follicular adenomas in 4/8 (50%) additional XP patients. DNA sequencing revealed rare mutations in two other XP patients with papillary thyroid cancer.

Conclusions XP patients have an increased incidence of thyroid nodules at an early age in comparison to the general population. These finding confirm another premature aging feature of XP.

Keywords DNA repair · Xeroderma pigmentosum · Thyroid cancer · Thyroid nodules · Thyroid ultrasound · DNA sequencing

Introduction

Xeroderma pigmentosum (XP) is a rare, autosomal recessive disease of DNA repair characterized by severe ultraviolet (UV) sensitivity resulting in a more than 10,000-fold increased risk for early age of onset skin cancer [1–4]. Symptoms include severe burns after minimal sun exposure (50% of patients). XP is considered a premature aging disease because of features including dry skin, increased sun-induced freckle-like pigmentation on sun exposed skin before age 2 years, skin cancers at an early age (median age 9 years), premature menopause and progressive sensorineural hearing loss with neurological degeneration [1–3, 5, 6]. Patients with XP have inherited germline mutations in genes involved in the DNA nucleotide excision repair (NER) pathway including *XPA, XPB/ERCC3, XPC, XPD/ERCC2, XPE/DDB2, XPF/ERCC4, XPG/ERCC5* or in the trans-lesion synthesis gene, *pol eta* [2].

Several studies of XP patients from North Africa (Libya, Tunisia, Morocco and Algeria) have described multiple thyroid nodules and thyroid adenocarcinomas in young XP patients with inherited mutations in the *XPC* gene [4, 7–10]. Thyroid nodules are recognized as a risk factor for cancer [11]. Age is an important prognostic indicator in the majority of staging systems for thyroid cancer [12].

We have studied the natural history of XP at the National Institutes of Health (NIH) since 1971. Due to early detection,

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good UV protection and improved medical care [13], XP patients appear to be experiencing fewer skin cancers and are living longer, thus permitting identification of clinical features that may develop later in life. XP patients have an approximately 50-fold increased risk of central nervous system cancers as well as reports of lung, hematologic and uterine neoplasms [1, 3, 4, 9, 10, 14, 15]. In view of the reports of thyroid nodules in young XP patients from North Africa, we studied medical records, clinical examinations and autopsies from all XP patients enrolled in our National Institutes of Health (NIH) cohort to evaluate the prevalence of thyroid nodules and thyroid cancer as indicators of premature aging.

Patients and methods

Study subjects

Our NIH cohort included 123 XP patients examined at the NIH Clinical Center from 1971 to 2019. They were studied under National Cancer Institute (NCI)-approved natural history protocols.

Thyroid ultrasound evaluation

Thyroid ultrasound scans were performed with a General Electric LOGIQ E10 or E9 ultrasound unit utilizing a 6–15 MHz linear array transducer. Patient thyroid ultrasound reports were accessed through the NIH digital record Clinical Research Information System (CRIS). The ultrasound scans were then reviewed by one radiologist (JM) to identify and characterize the presence of any thyroid nodules 2 mm or greater in size. Each thyroid nodule was classified for its risk for malignancy using the American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS) sonogram lexicon [16, 17]. This system assesses the risk for malignancy of a thyroid nodule on a scale from 1 to 5 based on its composition, echogenicity, shape, margin and echogenic foci (calcifications). A TI-RADS score of 5 represents the highest risk for thyroid nodule malignancy.

Thyroid tissue sequencing

Surgically excised, formalin-fixed, routinely processed, paraffin-embedded tissue blocks of thyroid cancers were obtained from patients who had thyroidectomies performed by their local surgeons. Histologic sections were reviewed by an NCI pathologist (C–CL) who identified the carcinoma-containing areas that were then micro-dissected. Mutations were identified with a next-generation sequencing-based assay (Oncomine™ Comprehensive Assay v3; Thermo Fisher Scientific), which was performed and analyzed as described previously [18].

Thyroid pathology in autopsy cases

Autopsies were previously performed on XP patients in the NIH natural history study by the NCI Department of Pathology [19–21]. Paraffin-embedded blocks of thyroid tissue from the autopsies were identified and the corresponding hematoxylin and eosin stained slides were reviewed by an NCI pathologist (C–CL) to identify thyroid nodules or other thyroid pathologies.

Comparison groups

Using the NIH Biomedical Translational Research Information System (BTRIS) electronic medical record system, we obtained de-identified thyroid reports from NIH patients who received a thyroid ultrasound scan at the Clinical Center and were diagnosed with thyroid nodules. This cohort consisted of 682 healthy volunteers and patients who were enrolled across a variety of studies conducted at the NIH from 1973 to 2019. The age range of this population was from 5 to 85 years. Thyroid nodule data were also obtained using the published comparison group of Smith-Bindman et al. from the University of California, San Francisco [22] and the published comparison group in the study of Moon et al. in South Korea [23].

XP complementation group determination

The XP complementation group was determined based on functional studies of DNA repair of cultured fibroblasts or of direct DNA sequencing from fibroblasts or peripheral blood mononuclear cells as described previously [24–26].

Results

During their visits to the NIH Clinical Center from 2011 to 2019 for diagnostic evaluation, the thyroid gland of all 29 XP patients entering the study was scanned by ultrasound for screening purposes. The ages of these XP patients ranged from 12 to 72 years. They had inherited mutations in the nucleotide excision repair genes, *XPA* [2; 7%], *XPC* [20; 69%], *ERCC2/XPD* [2; 7%], and the lesion bypass polymerase gene, *polymerase eta* XP variant [2; 7%]. The mutation was not known for three (10%) patients (Table 1).

Of the 29 XP patients who were examined with an ultrasound scan, 18 (62%) had thyroid nodules (Table 1). Most of these patients [14/18 patients, 78%] had mutations in the *XPC* gene. There were more females [13] than males [5]. This is similar to the preponderance of females with thyroid nodules in studies from the US [22] and from South Korea

Table 1 Xeroderma pigmentosum patients studied

Patient ID	Ultrasound at NIH?	Presence of thyroid nodules on ultrasound?	Age at last observation (yrs)	Sex	Complementation group	Skin cancer?/age at first cancer	Premature menopause?/Age	Thyroid comments
XP581BE	Yes	Yes	12	M	XPC	Yes/9	–	
XP338BE	Yes	Yes	15	M	XPC	No	–	
XP349BE	Yes	Yes	16	F	XPC	Yes/2	RP[3]	
XP580BE	Yes	Yes	17	F	XPC	Yes/8	RP	
XP579BE	Yes	Yes	19	F	XPC	Yes/5	RP	
XP198BE	Yes	Yes	20	F	XPC	Yes/8	RP	
XP576BE	Yes	Yes	22	M	XPC	Yes/28	–	
XP330BE	Yes	Yes	22	M	XPC	Yes/7	–	
XP63BE	Yes	Yes	25	F	XPC	Yes/5	RP	
XP415BE	Yes	Yes	25	F	XPC	Yes/3	Yes/30	
XP511BE	Yes	Yes	27	F	XPC	Yes/19	Yes/24	
XP600BE	Yes	Yes	27	F	Unknown	Yes/19	RP	
XP572BE	Yes	Yes	33	F	XPC	Yes/1.5	Yes/29	
XP517BE	Yes	Yes	35	F	C	Yes/10	Yes/35	
XP105BE	Yes	Yes	37	F	XPC	Yes/24	Yes/27	
XP224BE	Yes	Yes	43	F	Variant	Yes/10	RP	Fine needle aspirate—benign
XP516BE	Yes	Yes	49	F	Unknown	Yes/17	NM[4]	
XP31BE	Yes	Yes	72	M	Variant	Yes/9	–	
XP586BE	Yes	No	9	M	XPD	No	–	
XP419BE	Yes	No	11	F	XPC	Yes/10	RP	
XP358BE	Yes	No	12	F	XPC	Yes/2	RP	
XP591BE	Yes	No	12	F	Unknown	No	RP	
XP442BE	Yes	No	17	F	XPC	Yes/10	RP	
XP84BE	Yes	No	20	F	XPD	No	RP	
XP337BE	Yes	No	26	F	XPA	No	RP	
XP510BE	Yes	No	30	F	XPC	Yes/6	Yes/35	Thyroiditis
XP443BE	Yes	No	36	F	XPC	Yes/3	Yes/31	
XP607BE	Yes	No	38	M	XPA	Yes/29	–	
XP86BE	Yes	No	64	F	XPC	Yes/7	Yes/32	
XP540BE	No	n/a	9[1]	F	XPC	Yes/5	Yes/19	Surgery—multinodular goiter
XP570BE	No	n/a	24[1]	F	XPC	Yes/4	Yes/31	Surgery—papillary thyroid cancer
XP37BE	No	n/a	57[1]	F	XPE	Yes/7	NM	Surgery—papillary thyroid cancer
XP509BE	No	n/a	13[2]	M	XPA	No	–	Autopsy—normal thyroid
XP243BE	No	n/a	20[2]	M	XPC	Yes/18 mo	–	Autopsy—multinodular goiter + nodules of follicular adenoma
XP4BE	No	n/a	27[2]	M	Variant	Yes/9	–	Autopsy—metastatic melanoma left lobe of thyroid
XP24BE	No	n/a	35[2]	F	XPC	Yes/6	Yes/27	Autopsy—multinodular goiter + nodule of adenoma
XP30BE	No	n/a	38[2]	M	XPC	Yes/2	–	Autopsy—multinodular goiter + nodules of follicular adenoma
XP12BE	No	n/a	44[2]	F	XPA	Yes/8	RP	Autopsy—autolysis

Table 1 (continued)

Patient ID	Ultrasound at NIH?	Presence of thyroid nodules on ultrasound?	Age at last observation (yrs)	Sex	Complementation group	Skin cancer?/age at first cancer	Premature menopause?/Age	Thyroid comments
XP18BE	No	n/a	45[2]	F	XPD	Yes/9	RP	Autopsy—colloid filled nodules
XP1BE	No	n/a	49[2]	F	XPC	Yes/4	Yes/25	Autopsy—follicular adenoma

[1]Age at surgery—XP540BE also had mixed phenotype acute leukemia [21]

[2]Age at death—autopsy performed, cause of death—XP243BE—myelodysplastic syndrome; XP4BE—metastatic melanoma; XP24BE—glioblastoma; XP30BE—leukemia; XP12BE—neurologic degeneration, cachexia; XP18BE—neurologic degeneration; XP1BE—metastatic carcinoma of the uterus

[3]RP regular periods

[4]NM normal menopause

[23]. In patients with thyroid nodules, the number of nodules varied from 1 to 4 (Fig. 1). Multiple nodules were common and 67% (12/18) of the XP patients had 2–4 thyroid nodules (Fig. 1). Multiple thyroid micronodules whose sizes could not be measured by ultrasound were also a characteristic feature of some XP patients.

We estimated the malignant potential of each nodule by use of the American College of Radiology Thyroid Imaging, Reporting and Data System (ACR TI-RADS) sonogram lexicon [16]. This system assesses the risk for malignancy of a thyroid nodule on a scale from 1 to 5 based on its composition, echogenicity, shape, margin and echogenic foci (calcifications). A TI-RADS score of 5 represents the highest risk for thyroid nodule malignancy. The ages of the patients, their respective number of nodules and TI-RADS scores are shown in Fig. 1. There were two thyroid nodules with a TI-RADS score of 5 in a 25-year-old XP-C patient (XP415BE). One XP variant patient, a 43-year-old female (XP224BE), had a biopsy of an enlarging thyroid nodule that had a TI-RADS score of 4. Upon ultrasound-guided fine-needle aspiration cytopathology analysis, the nodule was reported to be benign. Patient XP540BE had a thyroidectomy for multinodular goiter at 9 years and 8 months of age. She was of North African ancestry with a homozygous founder mutation in the *XPC* gene [27]. She developed mixed phenotype acute leukemia at age 19 years [21].

A cumulative distribution graph was plotted to compare thyroid nodule prevalence by age among comparison groups and our XP population (Fig. 2). The median age of the 18 patients with thyroid nodules in our XP cohort (20 years) was younger than that of 3 comparison groups: 36 years (California study—208 subjects); 48 years (Korean study—24,757 subjects) and 52 years (NIH—682 subjects). Thus, these XP patients show early onset of thyroid nodules, a feature of premature aging.

Two patients (XP570BE and, XP37BE) had thyroidectomies for the removal of thyroid cancer (Table 1). Patient XP570BE, with mutations in the *XPC* gene, was diagnosed

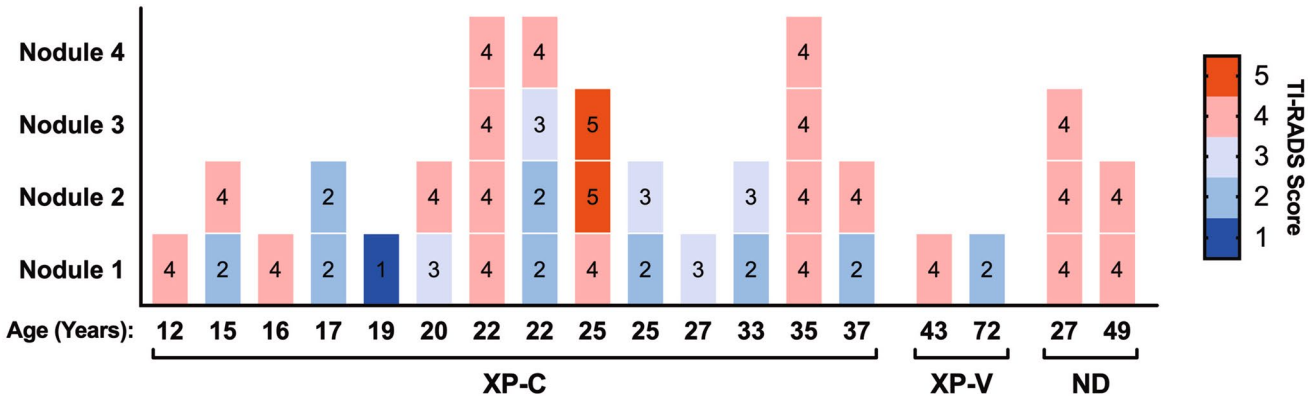

Fig. 1 Summary of ultrasound findings for XP patients with detectable thyroid nodules. A total of 18/29 patients examined by ultrasound scan had nodules. Nodule multiplicity and Thyroid Imaging Reporting and Data System (TI-RADS) score are reported for each patient, which are separated according to XP group and age. *XP-C* mutations in XPC, *XP-V* XP variant with mutations in pol eta, *ND* not determined

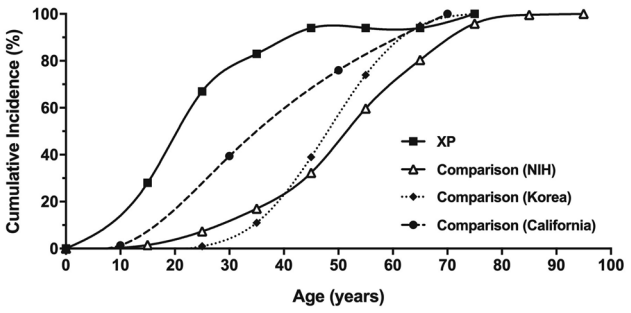

Fig. 2 Cumulative incidence of thyroid nodules across age categories in XP and comparison cohorts. XP patients, this study ($n=18$), filled squares; Comparison, NIH—BTRIS, NIH Biomedical Translational Research Information Systems, this study ($n=682$), open triangles; Comparison, Korea—Moon et al. [22] cohort from South Korea ($n=24{,}757$), filled diamonds; Comparison, California—Smith-Bindman et al. [21] cohort from University of California, San Francisco study ($n=369$), filled circles

with hypothyroidism and a goiter at 24 years of age. A thyroid ultrasound exam at her local medical care center revealed the presence of two thyroid cysts. Thyroidectomy found stage 1 papillary thyroid carcinoma. She was then treated with radioactive iodine. There was no recurrence with 10 year follow-up. She has a family history of thyroid abnormalities; her mother and sister had thyroiditis and received treatment. DNA sequencing of her thyroid tumor tissue at NIH revealed a *PTEN* exon 8 splicing acceptor site mutation (c.802-1G > T) that was predicted to be pathogenic and an *NF1* gene mutation (c.2159G > A) that was predicted to be likely pathogenic (Table 2).

Patient XP37BE, with inherited mutation in the *XPE/DDB2* gene [24], had a clinical history of multi-nodular thyroid. She was diagnosed with papillary thyroid carcinoma at 57 years of age after undergoing a thyroid ultrasound exam at her local medical care center as part of this study. DNA sequencing of the thyroid cancer at NIH revealed a likely significant mutation in the *FGFR4* gene (c.1949G > A) and a TFG(5)–NTRK1(10) fusion mutation interpreted as significant (Table 2).

To gain additional insight regarding the prevalence of thyroid abnormalities among our XP patients, we reviewed the thyroid tissue histology from the autopsies of eight XP patients in our cohort (two XP-A, four XP-C, one XP-D, and one XP-V) (Table 1). These patients died of internal malignancies (glioblastoma, adenocarcinoma of uterus, leukemia, myelodysplastic syndrome, or metastatic melanoma), neurologic degeneration or cachexia [19–21]. Five (65%) of the patients with autopsies (four XP-C and one XP variant) had thyroid abnormalities. Follicular adenomas were identified in four patients (50%) and multinodular goiter was present in three (38%) of them. One XP variant patient was reported to have a thyroid nodule 0.5 cm in diameter. One XP-A patient

Table 2 Small nucleotide and structural variants in thyroid tumors of two XP patients

Small nucleotide variants							
Patient ID	Gene	Genomic location	Transcript	Nucleotide change	Amino acid change	Pathogenicity assessment	Frequency in COSMIC[1]
XP540BE	*PTEN*	Chr10:89720650	NM_000314.8	c.802-1G > T	Exon 8 splice acceptor site variant	Pathogenic	14/1284 (1%)
	NF1	Chr17:29553610	NM_000267.3	c.2159G > A	p.Arg720Gln	Likely pathogenic	10/513 (1.95%)
XP37BE	*FGFR4*	Chr5:176523292	NM_213647.3	c.1949G > A	p.Arg650His	Likely significant	1/489 (0.2%)
Structural variants							
Patient ID		Gene/fusion		Interpretation			Frequency in COSMIC
XP37BE		TFG(5)-NTRK1(10) fusion		Significant			2/495 (0.4%)

[1]Catalogue of Somatic Mutations in Cancer (COSMIC), https://cancer.sanger.ac.uk/cosmic. Reported frequency of total point mutations detected in the indicated gene in papillary thyroid carcinoma tissue

had a histologically normal thyroid, while the other XP-A patient's thyroid gland was extensively autolysed by the time of autopsy. One XP-D patient had a hyperplastic nodule, characterized by follicular hyperplasia with abundant colloid. Because of the old age of the tissue blocks and autolysis, no tissue was suitable for performing DNA sequencing of the thyroid glands.

The XP patients in our study had other features of premature aging. Thirty-four of the 40 XP patients in this study had skin cancer (Table 1). The mean age of diagnosis of first skin cancer in these patients was 9 years, this is similar to the early age of onset of skin cancer reported in our earlier study [1]. This is more than 50 years younger than the age of onset of skin cancer in the general population [1]. There were 29 women in this study. Twelve of the women had premature menopause (range 19–35) defined as cessation of menses before age 40 years. This is another feature of premature aging in XP [5] (Table 1).

Discussion

XP is an extremely rare DNA repair disease with a prevalence of about 1 per million in the United States and Europe [28]. Patients have defective DNA repair and a markedly elevated risk of sunlight-induced skin cancer at an early age. About 20% of patients develop progressive neurodegeneration, including sensorineural hearing loss, dysphagia and ataxia at an early age [1, 6]. Our NIH natural history study of XP patients has given us the opportunity to follow and monitor these patients and identify the presence of thyroid nodules or other thyroid abnormalities.

Assessment of thyroid nodule prevalence in the general population has been reported to vary with the method of examination: 2–21% by palpation and 19–67% by ultrasound [29, 30] with prevalence increasing with age [29, 31]. Moon et al. [23] reported that the prevalence of thyroid nodules among 72,319 Korean subjects of mean age 49.5 ± 10.3 years who underwent a thyroid ultrasound was 34.2% ($n = 24{,}757$). This was lower than the frequency of thyroid nodules in our XP population (62%). In contrast, Smith-Bindman et al. [22] conducted a retrospective case–control study of 8806 consecutive patients who underwent thyroid ultrasound imaging at the University of California, San Francisco. Ultrasound examinations of 369 patients who did not have cancer identified thyroid nodules in 208 (56%). The frequency of thyroid nodules in this population was similar to that of our XP patients (62%). Multiple thyroid nodules (2–4) were present in 67% (12/18) of the XP patients with nodules. This is a similar frequency to that reported in older patients using ultrasound by Ezzat et al. [30] (45/67, 67%), and Smith-Bindman et al. [22] (125/208, 60%) but significantly higher ($p = 0.03$) than reported by Frates et al. [32] (804/1985, 41%). We detected thyroid nodules in 50% (4/8) of the XP patients who underwent autopsies. This is similar to the prevalence of thyroid nodules reported in other autopsy series for the general population (8–65%) (reviewed in [29]). As in the general population, women with XP were more likely to have thyroid nodules than males (Table 1) [22, 23, 30]. We detected thyroid nodules only in XP patients with XP-C, XP variant and unknown mutations.

Half of the XP patients with thyroid nodules had detectable nodules by 20 years of age (Fig. 2). This was younger than the median age of the patients with thyroid nodules in the studies of Smith-Bindman et al. [22] from California, Moon et al. [23] from South Korea, and NIH clinical research and volunteer studies at 36, 48, and 52 years, respectively. Similarly, studies of 123 young XP patients from North Africa (age 1–27 years) reported 10 (8%) patients with thyroid nodules [4, 7–9]. This early onset of thyroid nodules in the XP patients is a feature of premature aging in XP patients and suggests a role of DNA repair in the prevention of thyroid nodules. Other premature aging features of XP present in our patients (Table 1) include a 50 year reduction in age of onset of skin cancer compared to the general population [1] and premature menopause [5]. The XP patients also had early age of onset of photoaging of the skin [3], and several had progressive neurodegeneration [1, 6].

One of the limitations of this study was the small numbers of XP patients that were examined. Another was that we could not obtain data that reported the prevalence of thyroid nodules by age in the United States general population. Ezzat et al. used thyroid ultrasound to report a 67% ($n = 67$) prevalence of thyroid nodules among 100 healthy volunteers from Los Angeles, CA [30]. However, this study did not report the age of the individuals with nodules and the volunteers were not randomly selected. Thyroid nodules pose a low risk factor for developing thyroid cancer. The frequency of thyroid cancer found in a population of nearly 2000 subjects by use of fine needle aspiration of consecutively evaluated nodules > 10 mm in size approximates 8–15% [32]. The most recent estimates from the NCI Surveillance, Epidemiology and End Results (SEER) program are that there were more than 52,000 new cases of thyroid cancer in the US in 2019 with an estimated 2170 deaths. The lifetime risk of developing thyroid cancer is approximately 1.3% based on 2014–2016 data [33].

In the general population, the median age at diagnosis of thyroid cancer is 51 years and only 18% are diagnosed under the age of 35. Studies of 123 young XP patients from North Africa of age 1 to 27 years reported 5 (4%) patients with thyroid cancer [4, 7–9]. Two of the XP patients in our study developed thyroid cancer. One of them was at an early age (24 years old), the other at age 57 years. Both XP patients had the most common type of thyroid cancer, papillary carcinoma.

However, the mutations found in the XP patients' cancers were infrequently reported for papillary thyroid cancer in the Catalogue of Somatic Mutations in Cancer (COSMIC) database. Among the reported papillary thyroid mutations only 14 of 1284 (1%) were in *PTEN*, 10 of 513 (1.95%) in *NF1*, 1 of 489 (0.2%) in *FGFR4*, and a fusion mutation of TFG-NTRK1 was reported in 2 of 495 (0.4%) [34]. This fusion mutation may be amenable to drug treatment if it recurs [35]. In the general population, polymorphisms in the nucleotide excision repair genes *XPC* [36] and *ERCC2/XPD* [37] have been associated with small increases in thyroid cancer risk.

Physicians and other health professionals should consider examining the thyroid of XP patients to identify any thyroid abnormality. It is important for XP patients to be regularly monitored for any changes in their thyroid gland. Early detection and diagnosis of thyroid cancer can help prevent metastasis. This study suggests that DNA repair plays a role in prevention of thyroid nodules and provides further evidence of the relationship of DNA repair to premature aging phenotypes.

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Author contribution Concept, investigation, writing review and editing: all authors; software, visualization, and writing first draft: SDK, KHK; resources: JM, DT, CRL, JJD, KHK; supervision: JM, CRL, KHK; validation: DT, KHK; administration: KHK.

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Code availability Not applicable.

Compliance with ethical standards

Conflict of interest No conflicts of interest to declare.

Ethics approval This study was performed under National Cancer Institute (NCI)-approved natural history protocols.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The participants have consented to the submission of this report for publication.

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