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CANCER AND NEUROLOGIC DEGENERATION IN XERODERMA PIGMENTOSUM: LONG TERM FOLLOW-UP CHARACTERIZES THE ROLE OF DNA REPAIR

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Abstract

Background—We determined the frequency of cancer, neurologic degeneration and mortality in xeroderma pigmentosum (XP) patients with defective DNA repair in a four decade natural history study.

Methods—All 106 XP patients admitted to the NIH from 1971 to 2009 were evaluated from clinical records and follow-up.

Results—In the 65 percent (n=69) of patients with skin cancer, non-melanoma skin cancer (NMSC) was increased 10,000–fold and melanoma was increased 2,000-fold in patients under age 20. The 9 year median age at diagnosis of first non-melanoma skin cancer (NMSC) (n=64) was significantly younger than the 22 year median age at diagnosis of first melanoma (n= 38), a relative age reversal from the general population suggesting different mechanisms of carcinogenesis between NMSC and melanoma. XP patients with marked burning on minimal sun exposure (n=65) were less likely to develop skin cancer than those who did not. This may be related to the extreme sun protection they receive from an earlier age, decreasing their total UV

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exposure. Progressive neurologic degeneration was present in 24% (n=25) with 16/25 in complementation group XP-D. The most common causes of death were skin cancer (34%, n=10), neurologic degeneration (31%, n=9), and internal cancer (17%, n=5). The median age at death (29 years) in XP patients with neurodegeneration was significantly younger than those XP patients without neurodegeneration (37 years) (p=0.02).

Conclusion—This 39 year follow-up study of XP patients indicates a major role of DNA repair genes in the etiology of skin cancer and neurologic degeneration.

Keywords

genetic epidemiology; DNA repair; skin cancer; neurologic degeneration; xeroderma pigmentosum

INTRODUCTION

Evaluation of outcomes in patients with the neurocutaneous disorder, xeroderma pigmentosum (XP), has been limited by the number of individuals with this rare disorder and the heterogeneity of the clinical manifestations. XP is autosomal recessive with defects in repairing DNA damaged by ultraviolet radiation (UV) leading to a dramatically increased acute skin hypersensitivity to minimal sun exposure in some (Figure 1A), but not all (Figure 1B), patients and the development of non-melanoma skin cancer (NMSC) (Figure 1C) and melanoma at early ages [1–4]. Some XP patients also have progressive neurologic degeneration (Figure 1D) with some features of premature aging [2, 4–7]. XP is heterogeneous resulting from different defects in the nucleotide excision repair (NER) pathway [5, 8–11]. Seven XP complementation groups (genes), XP-A through XP-G, are associated with defective NER. The remaining group, XP variant, is deficient in DNA polymerase eta which is involved in translesional DNA synthesis.

We assessed the effects of defective DNA repair genes on the frequency of skin cancer, neurologic degeneration and mortality in XP patients examined at the National Institutes of Health (NIH) beginning in 1971 and ending in 2009. In addition, we examined the influence of genetic variations in melanocortin 1-receptor (MC1R), a gene strongly associated with human pigmentation, melanoma and NMSC in the general population [12–15] and in melanoma-prone families [16], on the risk of skin cancer in XP patients.

METHODS

DATA SOURCES

Data were abstracted from medical records at the Clinical Center, NIH; from medical records of outside institutions; from research records at the National Cancer Institute (NCI); from the Social Security Death Index; from previous publications; and from personally related information.

PATIENTS

We conducted a retrospective follow-up study of clinically confirmed XP patients initially examined by a co-author (KHK) at the NIH Clinical Center from 1971 to 2009. Patients were classified as having XP, XP/Cockayne syndrome complex (XP/CS), or XP with trichothiodystrophy (XP/TTD) as previously described [2, 4, 5, 7, 17]. Patients were generally referred by health care professionals. Informed consents were obtained under NCI Institutional Review Board-approved protocols in effect at enrollment.

END POINTS

Demographic and clinical data—The primary endpoints assessed were vital status, skin and other cancer occurrence, neurologic degeneration, and cause of death. Follow-up was obtained via telephone conversation with patients, family members, physicians, and review of the Social Security death index (http://ssdi.rootsweb.ancestry.com). Clinical data were collected using a standard questionnaire [3] completed at the time of the initial visit to NIH, medical records including pathology reports of skin and other cancers, patient photographs, research records, and published reports [1–5, 7, 18–46]. Only cancers validated by pathology report review were included. Variables collected included vital status, age, sex, ethnicity, age at first skin cancer, number and types of skin and other cancers XP [2, 4, 5, 7, 42] and non-XP type neurologic abnormalities, and cause of death.

Melanocortin-1 Receptor (MC1R) variations—A family- based case-control study was conducted on a subset of subjects having appropriate DNA samples to evaluate the relationships between *MC1R* variants in XP patients compared to unaffected family members. Sequencing of the 951 base pair *MC1R* coding region was performed at the Laboratory of Molecular Technology, SAIC, Frederick, MD as described previously [16]. Variants were detected using Mutation Surveyor (SoftGenetics Inc., PA) and SAIC sequence analysis software.

XP complementation group status—XP complementation group assignment was performed using cell fusion, host cell reactivation, western blotting or DNA sequencing [4, 19–21, 23, 25–27, 29, 32–36, 38, 44, 46, 47].

STATISTICAL ANALYSES

Cancer risk and mortality—For comparison to general population rates of cancer or mortality, follow-up began at birth, and ended on the date of diagnosis of cancer for the cancer rates, date the patient was last known to be cancer free (for cancer outcome), date of death for the mortality analyses, date last known to be alive (for mortality), or the end of follow-up (December 31, 2009), whichever came first. The observed number of NMSC was compared to the expected number from the Kaiser Permanente skin cancer database [48] after adjustment for age, sex, race, and birth cohort. The observed number of melanoma skin cancers was compared with the expected number in the general population (O/E ratio) based on the NCI Surveillance, Epidemiology, and End Results (SEER) cancer database [49].

The relative risk for each cause of death was estimated by calculating the standardized mortality ratio (SMR) and the exact Poisson 95% confidence interval (CI). The expected number of deaths was calculated by applying the US mortality rates (by 5-year age, 5 calendar year, and sex-specific categories) to the appropriate person-time accrued by XP survivors in the cohort [50]. Kaplan-Meier estimates were used to compare survival between different groups. PROC LIFETEST of SAS (Version 9.1.3) was used to test for differences in survivor function using the Wilcoxon test. Results with $p<0.05$ were regarded as significant. All statistical tests were two-sided.

MC1R and skin cancer risk—We evaluated each *MC1R* variant individually comparing 1+ variant to the consensus *MC1R* sequence. Because many *MC1R* variants were too rare to examine their individual associations with skin cancer risk, we also used the following *MC1R* variables in the analyses: carriers of any *MC1R* variant compared with wild-type *MC1R*; carriers of multiple (1,2+) variants compared with the consensus sequence; carriers of 1 non-red hair color (NRHC) variant. 2+ NRHC variants, 1 red hair color variant (RHC), 2+ RHC variants, or carriers of both RHC and NRHC variants compared with wild-type *MC1R*[16]. We also examined whether *MC1R* variants influenced the number of skin

cancers the patient had as well as whether the number of *MC1R* variants influenced the age at diagnosis of the patient's first skin cancer. Chi-square and Fisher exact tests were used to measure the association between skin cancer risk and RHC variables. The nonparametric Jonckheere-Terpstra test [51] was used to test the hypothesis of no differences among the ages at diagnosis of skin cancer according to number or type of *MC1R* variants against the alternative that the ages at diagnosis decreased as number or type of *MC1R* variants increased.

RESULTS

Study Demographics

All 106 XP patients examined at the NIH Clinical Center from 1/1971 through 12/2009 were included in this retrospective study (Table 1). Of these, 97 were classified as XP, 2 as XP/CS complex and 7 as XP/TTD; 78 were non-Hispanic whites (NHW). The median age at last observation or death was 26 years. The age at the last NIH visit was used for the 3 patients who were lost to follow-up. Always/sometimes burning on minimal sun exposure was reported in 63% of the patients (n=65) (Table 1, Figure 1A and online Table 1).

Complementation group assignments were determined for 100 of the patients [4, 19–21, 23, 25, 27–29, 32–36, 38, 41, 42, 44, 46] and unpublished observations (Table 1 and online Table 1). XP-C was the most common complementation group (43%, n=46) followed by XP-D (n=30). No XP-F or ERCC-1 patients were examined at NIH although defects in these genes were identified in cell lines from patients with late onset severe neurological degeneration who were not seen at NIH [52]. As we reported previously, [25] cells from 6 XP patients could not be assigned to any of the known complementation groups and may thus have defects in presently unidentified genes.

Skin Cancer Analysis

Sixty-nine patients (65%) had one or more skin cancers and 64 of these patients had NMSC (Table 1, Figure 2, 3 and online Table 1). Some patients had hundreds of primary skin cancers; for example we reported that patient XP29BE had 284 BCC, 12 SCC, and 24 melanomas documented histologically [20, 44]. Melanoma was diagnosed in 38 patients; 33 of these also had NMSC (Table 1, Figure 2). The NMSC preceded or was diagnosed at the same time as the melanoma in 29 of the 31 patients where age at first NMSC and melanoma was known (Figure 3B).

Among the XP patients, the median age at diagnosis of first NMSC was 9 years (range: 1–32 years). The median age at diagnosis of first melanoma (22 years, range: 2–47 years) was significantly older than NMSC ($p<0.001$). The age at diagnosis of XP skin cancer was substantially reduced compared to the general population: NMSC (median age 67 years) and melanoma (median age 55 years) (Figure 2A, 2B). There were 57 XP patients diagnosed with NMSC under the age of 20 years, producing a relative risk about 10,000 [95% CI 7,388 – 12,639] (Table 2) times the US population. Similarly, there were 14 XP patients diagnosed with melanoma under the age of 20 years, resulting in a relative risk more than 2,000 [95% CI 1,027–3,154] (Table 2) times the US population.

NMSC was present in 60% of the NHW patients (Table 1) (median age at diagnosis-9 years, n=47). Similarly 44% of the African/African American (A/AA) patients had NMSC (median age-12 years, n=7) ($p=0.8$). Two A/AA patients (but no NHW patients) had SCC of the anterior tongue ($p=0.04$). No skin melanomas were diagnosed in the A/AA patients ($p=0.1$).

By age 13 years, 50% of the patients had developed skin cancer (Figure 3A). When stratified by burning phenotype, those XP patients that never burned were more likely to be diagnosed

with skin cancer at an earlier age than those who had a history of always or sometimes burning on minimal sun exposure (p=0.006) (Figure 3C). This difference was also found for age at first NMSC and age at first melanoma. Many patients in complementation group XP-C, XP-E and variant never burned but were more likely to have skin cancer than patients in complementation groups XP-A, XP-B, XP-D and XP-G (p<0.001) (Figures 1B, 1C and 3D, Online table 1). Some of the XP-D and XP-A patients had severe blistering burns after a few minutes sun exposure (Figure 1A) but this extreme sun sensitivity was not reported for XP-C patients.

Neurological status

Progressive neurologic degeneration was observed in 25 (24%) XP patients. This included loss of intellectual functioning, deterioration of neurologic status, impaired hearing, abnormal speech, areflexia, ataxia, peripheral neuropathy, and loss of ability to walk and talk. Pathologically this is due to a primary neuronal loss reflected as cortical atrophy and dilated ventricles on MRI [2, 4, 5, 7, 42]. Patients with progressive neurologic degeneration were primarily in complementation group XP-D (n=16) and XP-A (n=6) (Online table 1). Two patients had XP/CS complex with skin features of XP and neurological degeneration of CS including retinal degeneration with defects in the *XPB* and *XPG* genes[4, 7, 33, 35, 36] (Table 1). Ten patients had non-XP related neurologic abnormalities; these included XP-C patients with hypoglycinemia [26, 37], with hearing loss and intellectual impairment without loss of coordination [28] or with neurological disorders and systemic lupus erythematosus [53].

Patient Mortality

Table 3 shows causes of death for the 29 XP patients who died. The median age of death was 32 years. XP survival rates were significantly lower than in the general population (p<0.001) (Figure 3E). The major causes of death were skin cancer (34%, n=10), neurologic degeneration (31%, n=9), and internal cancer (17%, n=5). Six deaths were secondary to metastatic melanoma (SMR=14, 95% CI=3–25), and 4 were secondary to invasive SCC (SMR=38, 95% CI=1–75). The SMR of death from internal cancers was 16.4 (95% CI 4.3 – 28.6). All 6 internal cancers occurred in patients who also had many skin cancers. There were 3 central nervous system cancers (SMR=11, 95% CI=1–23), and a peripheral nerve cancer (Table 3). [22]. These occurred in XP-C patients who had no neurological abnormalities. We previously reported that patient XP3BE, who died from lung cancer at age 37 years, had smoked cigarettes since age 18 years and also had many skin cancers and metastatic melanoma [3, 4, 41]. Similarly, our patient XP1BE had more than 100 skin cancers including NMSC and melanomas but died at age 49 years from metastatic endocervical adenocarcinoma of the uterus [4, 39, 42].

XP patients with neurologic degeneration had poorer survival rates than those patients who had no neurologic degeneration. The median age at death (29 years) in XP patients with neurological degeneration was significantly lower than those XP patients without neurological degeneration (37 years) (p=0.02; Figure 3F). The median age at death was 32 years in XP patients with defects in complementation groups that tended to be associated with neurologic degeneration (complementation groups XP-A, XP-B, XP-D and XP-G) compared to age 37 years in XP patients with defects in complementation groups less associated with neurologic degeneration (XP-C, XP-E and variant) (p=0.05). Deaths in patients with defects in the *XPC* gene were predominantly from cancer (metastatic or locally invasive skin cancer or nervous system cancers). In contrast, deaths in patients with defects in the *XPD* gene were predominantly related to progressive neurologic degeneration despite having large numbers of skin cancers.

MC1R Analysis

We included 79 XP patients (cases) and 101 unaffected XP heterozygotes/family members (controls) in analyses of the role of *MC1R* variants on the risk of skin cancer. As noted in previous studies of the general population [54–56], NHW had the majority of *MC1R* variants among these XP families (Online table 2).

There were no significant differences in the number or types of *MC1R* variants between cases and controls for any of these comparisons for all subjects or for NHW subjects (data not shown). *MC1R* variants were not associated with the occurrence of skin cancer in XP patients (all or NHW only), the number of skin cancers (single vs multiple), or the type of skin cancers (NMSC vs melanoma) (data not shown). Contrary to expectation, patients with RHC variants were significantly older at first melanoma diagnosis than those that did not have RHC variants (age=32 years, n=5, vs age=22 years, n=15; p=0.01); however, these data involved only a 20 patients with melanoma. Overall this small study of XP patients suggests that defective DNA repair has a greater influence on skin cancer risk than variants of MC1R.

DISCUSSION

In 1968 James Cleaver reported defective DNA repair in XP [57]. At NIH, Jay Robbins then initiated a study to evaluate XP patients; Kenneth Kraemer joined the study in 1971 and has led it for decades. We report an up to 39 year follow-up including 15 patients reported in 1974 [4] plus additional patients through 2009. We found a >10,000 fold increased risk of NMSC and >2,000 fold increased risk of melanoma under age 20. These rates, which vary somewhat from our earlier studies that included some of these patients [1, 3], are based on longer follow-up and increased numbers, thus contributing substantially more person years at risk The occurrence of UV type mutations in the tumor suppressor genes p53 in NMSC [58] and PTEN in melanomas [59] provide molecular evidence of a direct effect of UV exposure in skin cancer in XP patients. Compared to the general population [48, 60–63], the XP patients had a 58-year reduction in age at first NMSC, and a 33-year reduction in age at first melanoma. As in the general population, we found that the anatomic site distribution of NMSC in the XP patients was different from that of melanomas [3]. These differences suggest differences in mechanisms of carcinogenesis between NMSC and melanoma and emphasizes the importance of DNA repair in the protection against NMSC. Indeed, we found that XP-C patients with only a few percent of normal *XPC* mRNA resulting from a splice lariat mutation have a lower frequency of NMSC skin cancer than other XPC patients with different splice mutations leading to undetectable levels of *XPC* mRNA [46, 64].

Acute ultraviolet (UVB) exposure of the skin produces sunburn, an inflammatory response with erythema and blistering characterized histologically by a mixed dermal neutrophilic and lymphocytic infiltrate [65]. In the general population sunburning is a skin cancer risk factor [66]. Surprisingly, 38 of the XP patients reported never burning but these XP patients were more likely to be diagnosed with skin cancer at an earlier age than the 61% who had a history of always/sometimes burning on minimal sun exposure. This may be partly related to early initiation of rigorous sun protection because XP patients often experience severe blistering sunburn on minimal exposure (Figure 1A) (primarily in XP-A and XP-D). XP patients in complementation groups XP-A, XP-B, XP-D and XP-G (those with higher frequency of neurologic disease) were more likely to develop skin cancers at a later age than those patients in complementation groups (XP-C, variant) with no neurologic disease. These patients may also have less mobility. Many XP-C patients did not report burning on minimal sun exposure but tan normally and develop freckle-like pigmentation at an early age followed by skin cancer [28]. Similarly, mice with a defect in the *XPC* gene do not burn on minimal UV exposure [67]. Fibroblasts from XP patients with a history of sunburning on minimal exposure (in XP-A and XP-D) were reported to be more sensitive to killing by UV

than fibroblasts from XP patients who did not burn easily [18, 39]. It is thus possible that transcription coupled DNA repair (which is defective in XP-A and XP-D but not XP-C) [11] mediated cytokine generation [24, 43, 68] may play a major role in generation of the inflammatory sunburn response.

The role of pigmentation in protection from skin cancer is complex. In agreement with other studies of A/AA patients [69–71], cancers occurred on less pigmented sites, including the anterior tongue, at a greater frequency than in the NHW patients.[1, 3, 32] This sun-exposed site is an extremely unusual location for tongue neoplasms [72]. Perhaps the dark skin offers some protection despite defective DNA repair; thus these patients may experience greater sun exposure than lighter skinned patients. The frequency of NMSC in A/AA (3/100,000) is about 100-fold lower than in NHW [73]. In contrast, in A/AA XP patients the frequency of NMSC (44%) was not significantly different than NHW patients (61%). Thus a normally functioning DNA repair system may provide greater protection from NMSC than the dark pigmentation present in A/AA skin.

The most common cause of death was skin cancer (metastatic melanoma or invasive SCC). Despite an early age of skin cancer diagnosis, ~45% live into their 40's and the oldest patient died at age 73 years. As reported by others [58, 74] we found an increased mortality rate from CNS tumors in patients with defects in the *XPC* gene who did not have XP neurological degeneration. There is some evidence that these tumors may result from exposure to oxidative damage [58, 74]. Lung cancer was present in two cigarette-smoking patients which may be a consequence of the hypersensitivity of XP cells to mutagenic effects of components of cigarette smoke [11].

Progressive neurologic degeneration, which may have resulted from primary degeneration of previously normally developed neurons [5–7], was a major cause of death among the 25% of the susceptible patients (in XP-D, XP-A, XP-G and XP-B). Fibroblasts from XP patients with neurological degeneration were reported to be more sensitive to killing by UV than cells from XP patients without neurological degeneration [18, 40]. These findings implicate a role for DNA repair in maintenance of the viability of neurons.

Specific variants of the pigmentation related gene, *MC1R*, are associated with increased UV-induced erythema response [75] and increased risk of both melanoma and NMSC [12–15] in the general population, and in families with mutations in the melanoma susceptibility gene, *CDKN2A* [16]. In contrast, based on limited data, *MC1R* variants do not appear to dramatically affect the risks of skin cancer in individuals with XP.

Patients ascertained for this NIH study may not reflect the general population of XP patients. Many of our patients have been sun protected from very early ages, which could influence their subsequent development of skin cancer. This 39 year study characterizes the major morbidity and mortality of XP and suggests a major role of DNA repair in the etiology of skin cancer and neurologic degeneration.

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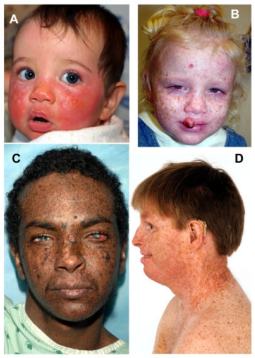

Figure 1.

XP patients in study. A) Patient XP420BE complementation group XP-D at 9 months of age with severe blistering erythema of the malar area following minimal sun exposure. Note sparing of her forehead and eyes that were protected by a hat. B) Patient XP358BE (XP-C) at age 2 years did not sunburn easily but developed multiple hyperpigmented macules on her face. A rapidly growing SCC or keratoacanthoma grew on her upper lip and a pre-cancerous lesion appeared on her forehead. C) Northern African patient XP393BE (XP-C) [32] at age 23 years with numerous hyperpigmented macules on his face. Nodular basal cell cancer is present on his left nasal root. Pigmented basal cell cancer is present on his left cheek. His eyes show cornea scarring from unprotected sun exposure. D) Patient XP19BE (XP-A) [45] at age 35 years with neurological degeneration. He has numerous hyperpigmented macules on sun exposed areas of his face and neck. Progressive sensorineural deafness requires use of a hearing aid.

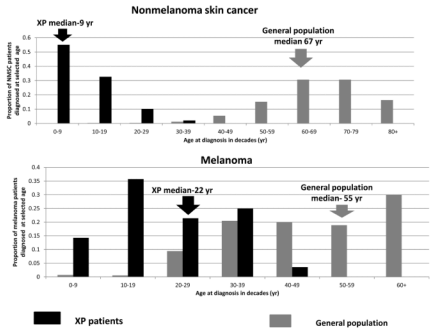

Figure 2.

XP skin cancer by age at first skin cancer diagnosis and skin cancer type compared to U.S. general population. A. Proportion of NMSC patients diagnosed at selected ages. B. Proportion of melanoma patients diagnosed at selected ages. Individuals with both NMSC and melanoma were used for both analyses. General population data taken from [48].

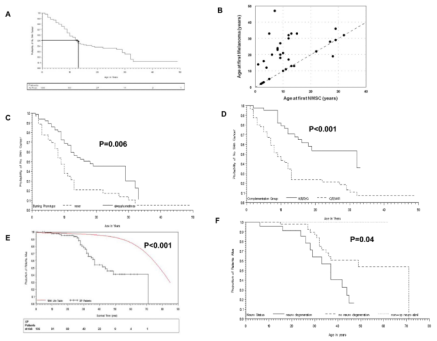

Figure 3.

Skin cancer and mortality in XP patients. A. Probability of the absence of skin cancers for all XP patients (n=106). At age 12 years, 50% of the patients had been diagnosed with NMSC or melanoma skin cancer (arrows) B. Scatter plot age of diagnosis of first skin cancer in patients with both NMSC and melanoma. NMSC was diagnosed earlier or at the same time as melanoma in 29/31 patients.. C. Probability of the absence of skin cancer stratified by burning phenotype. Patients that "never" burned on minimal sun exposure (n= 38) were significantly more likely to develop NMSC or melanoma skin cancer at an earlier age than those that "always or sometimes" burned (n=65) on minimal sun exposure (p=0.006). D. Probability of the absence of skin cancer stratified by XP complementation group. Patients in complementation groups XP-A, XP-B, XP-D and XP-G developed skin cancer at a significantly older age than those in complementation groups XP-C, XP-E and variant (p=0.009). E. Kaplan Meier curve of xeroderma pigmentosum patient survival compared to US general population. 30% of XP patients had died by age 32. The survival of the XP patients was significantly less than the general population (p<0.001). F. Kaplan Meier curve of xeroderma pigmentosum patient survival stratified by neurologic phenotype. Patients with neurologic degeneration had poorer survival rates than those without neurologic degeneration (p=0.04).

Table 1

Xeroderma pigmentosum patients at the NIH, 1971–2009

		Gender		Race/Ethnicity				
	Total	**Male**	**Female**	**NHW**	**African/AA**	**Asian**	**HW**	**NA**
Total	106	48	58	78	16	4	6	2
Age at Last Observation/Age at Death								
Mean	28	27	28	30	24	16	21	23
Median	26	22	28	29	22	17	16	23
Youngest	1	4	1	1	5	8	7	14
Oldest	73	73	57	73	57	21	45	31
Burning phenotype								
Always/sometimes	65	24	41	52	9	1	3	0
Never	38	23	15	25	5	3	3	2
Unknown	3	1	2	1	2	0	0	0
Complementation Group (Phenotype)								
A (XP)	10	5	5	6	3	1	0	0
B (XP/CS)	1	0	1	1	0	0	0	0
C (XP)	46	24	22	28	8	3	5	2
D (XP)	23	8	15	18	3	0	1	0
D (XP/TTD)	7	3	4	7	0	0	0	0
E (XP)	3	1	2	3	0	0	0	0
G (XP)	2	1	1	1	1	0	0	0
G (XP/CS)	1	1	0	1	0	0	0	0
Variant (XP)	7	4	3	7	0	0	0	0
Unknown[a] (XP)	6	1	5	5	1	0	0	0
Skin cancer?								
Yes	69	31	38	52	7	4	4	2
No	33	15	18	22	9	0	2	0
Unknown	4	2	2	4	0	0	0	0

		Gender		Race/Ethnicity				
	Total	**Male**	**Female**	**NHW**	**African/AA**	**Asian**	**HW**	**NA**
Type of Skin Cancer								
NMSC	64	29	35	47	7	4	4	2
Melanoma	38	20	18	34	0	1	2	1
Neurologic phenotype								
Degeneration present	25	12	13	21	4	0	0	0
No degeneration	70	31	39	50	9	3	6	2
Non-XP neuro abnormality	10	5	5	6	3	1	0	0
Unknown	1	1	1	1	0	0	0	0

[a] Six patients were tested for complementation groups and did not have A, B, C, D, E, F, G, ERCC1 or Variant defects

Abbreviations: NHW-Non Hispanic Whites; AA-African Americans; HW-Hispanic Whites; NA-Native Americans XP-Xeroderma pigmentosum, CS-Cockayne syndrome, TTD-Trichothiodystrophy; NMSC-nonmelanoma skin cancer

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Table 2

Observed/Expected rates of skin cancer in XP patients by age

Attained Age	Selected Events	Observed	Expected	O/E[#]	95% CI Lower	95% CI Upper
<10	All Skin Cancers	40	0.01[+]	5,434	3,882	7,400
<10	NMSC	36	0.00[+]	11,139	7,802	15,421
<10	Melanoma	4	0.00[+]	969	264	2,480
10–19	All Skin Cancers	31	0.01[+]	5,229	3,553	7422
10–19	NMSC	21	0.00[+]	8,043	4,979	12294
10–19	Melanoma	10	0.00[+]	3,014	1,446	5544
20–39	All Skin Cancers	26	0.11[+]	239	156	351
20–39	NMSC	7	0.01[+]	525	211	1082
20–39	Melanoma	19	0.10[+]	199	120	311
Total	All Skin Cancers	98	0.37[+]	264	214	322
Total	NMSC	64	0.20[+]	327	252	418
Total	Melanoma	34	0.18[+]	193	134	270

[#] all values were $P < 0.05$

[+] The required age or year was not found in the referent rate table, therefore the closest age/year was used to obtain the rate.

Table 3

Xeroderma pigmentosum patient deaths, 1971–2009

XP Number	Comp Group	Phenotype	Age at Death (yr)	Cause of Death	Reference
XP20BE	G	XP/CS[a]	6	Neurological degeneration	[7, 33, 36]
XP422BE	UNK	XP	11	Metastatic melanoma	This study
XP286BE	D	XP	16	Neurological degeneration	This study
XP15BE	C	XP	16	Glioblastoma	[3, 4]
XP120BE	A	XP	24	Neurological degeneration	This study
XP13BE	VAR	XP	25	Struck by lightning	[4, 18]
XP17BE	D	XP	26	Neurological degeneration	[18]
XP4BE	VAR	XP	27	Metastatic melanoma	[4, 18, 76]
XP5BE	D	XP	28	Neurological degeneration	[4, 18]
XP423BE	UNK	XP	28	Invasive SCC	This study
XP10BE	C	XP	28	Invasive SCC	[4, 18]
XP6BE	D	XP	29	Invasive SCC/Neurological degeneration[b]	[4, 18, 20]
XP424BE	C	XP	29	Metastatic melanoma	This study
XP23BE	C	XP	31	Metastatic melanoma/astrocytoma cord[c]	[3, 22, 24, 27, 31]
XPTTD384BE	D	XP/TTD[a]	32	Metastatic melanoma	This study
XP27BE	C	XP	32	Unknown	[77]
XP8BE	C	XP	32	Metastatic melanoma	[4]
XP26BE	C	XP	33	Invasive SCC	This study
XP11BE	B	XP/CS[a]	33	Arteriosclerosis	[4, 35]
XP24BE	C	XP	35	Glioblastoma	[24, 31, 59]
XPLABE	D	XP	36	Drug overdose	[78]
XPBHBE (XP1MI)	C	XP	37	Unknown	[53]
XP3BE	C	XP	37	Lung cancer/Metastatic melanoma[d]	[3, 4, 18, 41]
XP29BE	D	XP	37	Neurological degeneration	[44, 59]
XP7BE	D	XP	42	Neurological degeneration	[4, 18]
XP12BE	A	XP	44	Neurological degeneration	[4, 18, 24, 31, 45, 45, 79]

XP Number	Comp Group	Phenotype	Age at Death (yr)	Cause of Death	Reference
XP32BE	D	XP	46	Neurological degeneration	This study
XP1BE	C	XP	49	Uterine cancer	[4, 18, 24, 27, 39, 41, 41, 42, 59]
XP14BE	C	XP	73	Schwannoma	[4]

[a] XP/CS indicates Xeroderma pigmentosum/Cockayne syndrome complex. XP/TTD indicates Xeroderma pigmentosum/Trichothiodystrophy

[b] XP6BE died from invasive SCC; however, the patient also had neurologic degeneration

[c] XP23BE died from metastatic melanoma; however, the patient also had astrocytoma of spinal cord

[d] XP3BE died from lung cancer; however, the patient also had metastatic melanoma