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Increased Cancer Risks in Myotonic Dystrophy

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Abstract

Objective: To estimate cancer risks for patients with myotonic dystrophy, given that increased risks for neoplasms in association with myotonic dystrophy type 1 and type 2 have been suggested in several studies but the risks of cancers have not been quantified.

Patients and Methods: A cohort of 307 patients with myotonic dystrophy identified from medical records of Mayo Clinic in Rochester, MN, from January 1, l993, through May 28, 2010, was retrospectively analyzed. We estimated standardized incidence ratios (SIRs) of specific cancers for patients with myotonic dystrophy compared with age- and sex-specific cancer incidences of the general population. Age-dependent cumulative risks were calculated using the Kaplan-Meier method.

Results: A total of 53 cancers were observed at a median age at diagnosis of 55 years. Patients with myotonic dystrophy had an increased risk of thyroid cancer (SIR, 5.54; 95% confidence interval [CI], 1.80-12.93; $P=.001$) and choroidal melanoma (SIR, 27.54; 95% CI, 3.34-99.49; $P<.001$). They may also have an increased risk of testicular cancer (SIR, 5.09; 95% CI, 0.62-18.38; $P=.06$) and prostate cancer (SIR, 2.21; 95% CI, 0.95-4.35; $P=.05$). The estimated cumulative risks at age 50 years were 1.72% (95% CI, 0.64%-4.55%) for thyroid cancer and 1.00% (95% CI, 0.25%-3.92%) for choroidal melanoma. There was no statistical evidence of an increased risk of brain, breast, colorectal, lung, renal, bladder, endometrial, or ovarian cancer; lymphoma; leukemia; or multiple myeloma.

Conclusion: Patients with myotonic dystrophy may have an increased risk of thyroid cancer and choroidal melanoma and, possibly, testicular and prostate cancers.

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Myotonic dystrophy (dystrophia myotonica) is initially a clinically defined disorder and is commonly characterized by myotonia, progressive muscle weakness, and onset of cataracts at a young age.[1] Molecular genetic studies have identified 2 types of myotonic dystrophy (summarized in Table 1): myotonic dystrophy type 1 (Online Mendelian Inheritance in Man [OMIM] 160900), which is caused by an unstable CTG trinucleotide repeat expansion in the 3′ untranslated region of the *DMPK* gene,[2-6] and myotonic dystrophy type 2 (OMIM 602668), which is caused by an unstable CCTG tetranucleotide repeat expansion in intron 1 of the *CNBP (ZNF9)* gene.[7-9] Approximately 1 in 8000 people have myotonic dystrophy,[10] and the prevalence appears to differ in various geographic and ethnic populations.[11-16] The proportions of myotonic dystrophy type 1 and type 2 are unknown, but myotonic dystrophy type 1 has been reported to be more common than type 2 in most populations.[10]

There have been several studies and case reports on both benign and malignant neoplasms in patients with myotonic dystrophy. Pilomatricomas are the most commonly reported neoplasms. A variety of other neoplasms have been described, including thymoma; basal cell carcinomas; insulinomas; leukemia; lymphoma; spinal hemangioblastoma; maxillary jaw odontoma; adenomas of the parotid, parathyroid, thyroid, and pituitary glands; and cancers of the stomach, colon, testis, ovary, kidney, larynx, and thyroid. Tumors were first diagnosed, on average, in patients 44 years of age.[17] To our knowledge, risks of cancers in patients with myotonic dystrophy have not been quantified.

PATIENTS AND METHODS

Identification of Patients

The electronic medical records of Mayo Clinic in Rochester, MN, from January 1, l993, through May 28, 2010, were text-word searched for the term *myotonic dystrophy*, identifying 1687 unique medical records. The medical records were then abstracted individually to confirm a diagnosis of myotonic dystrophy. A total of 307 patients had a confirmed diagnosis based on (1) a positive genetic test result in that individual (expansion mutation within *DMPK* or *CNBP*), (2) a positive gene test result in a blood relative plus a clinical picture of myotonic dystrophy in the patient even if a gene test was not performed, or (3) a clinical diagnosis alone established by consultation with a neurologist plus relevant laboratory findings. We were not able to determine from this chart review how many unique families were represented by these 307 patients. Most patients had a comprehensive consultation in one or more departments, and all patients completed a

TABLE 1. Comparison of Clinical and Genetic Features of Myotonic Dystrophy Type 1 and Type 2

	Type 1	Type 2
Synonyms	DM1, Steinert disease	DM2, proximal myotonic myopathy (PROMM), Ricker syndrome
Causative gene	*DMPK*	*CNBP (ZNF9)*
Chromosomal location	19q13.3	3q21
Mutation	Unstable trinucleotide (CTG) expansion in 3′ untranslated region of messenger RNA that is expressed in tissues of affected individuals	Unstable tetranucleotide (CCTG) expansion in intron 1 (75-11,000; mean, 5000 repeats) in *CNBP*
Inheritance	Autosomal dominant	Autosomal dominant
Myotonia	+	+
Muscle weakness	+	+
Cataracts	+	+
Muscle/joint pain/stiffness	-	+
Muscle atrophy	+	+/-
Calf hypertrophy	-	+/-
Cardiac arrhythmias	+	+/-
Elevated serum creatine kinase level	+	+
Hypoimmunoglobulinemia	+	+/-
Tremors	-	+/-
Late change in cognition	+	+/-
Hypersomnia	+	+/-
Mental retardation	+/-	-
Insulin resistance/diabetes	+	+/-
Male hypogonadism	+	+/-
Frontal baldness	+	+/-

medical history intake form. This study was approved by the Mayo Clinic Institutional Review Board, and patients gave consent for use of their medical records for research.

Statistical Analyses

Observation time for each patient started at birth and ended at the age at first diagnosis of cancer or last contact or death, whichever occurred first. Cancer-specific standardized incidence ratios (SIRs) were calculated by dividing the observed numbers of cancers by the expected numbers. Ninety-five percent confidence intervals (CIs) were calculated by exact methods, assuming Poisson distribution of observed cases. The expected numbers of cancers were calculated by multiplying the age- and sex-specific incidence for the US general population with the corresponding observation time in the study cohort. We obtained age- and sex-specific US cancer incidences in 1998-2002 from the Surveillance, Epidemiology, and End Results (SEER) 14 registries.[18] For patients with missing ages at cancer diagnoses (n=5; 3 nonmelanoma skin cancers and 2 prostate cancers), age at diagnosis was assumed to be 1 year before the last known age. Kaplan-Meier failure function was used to estimate cumulative risk (penetrance) at ages 50 and 70 years. All reported statistical tests were 2-sided, and $P<.05$ was considered statistically significant. All statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX).

RESULTS

The study comprised 307 patients with myotonic dystrophy (54% female) who were identified from medical records of Mayo Clinic in Rochester, MN, and were included regardless of cancer status or family history of cancer. Of all patients with myotonic dystrophy in this study, 118 were type 1 (74 were verified by genetic test in our records) and 86 were type 2 (45 were verified by genetic test in our records). The remainder of these groups were assigned on the basis of genetic tests conducted elsewhere and cited in the medical record or known to be positive in a blood relative. For 103 patients, no genetic testing was reported to have been done in the patient or in any affected relative, but the clinical diagnosis was well established (Table 2).

TABLE 2. Baseline Characteristics of Patients With Myotonic Dystrophy (N=307)

Characteristic	No. (%) of patients
Sex	
Male	142 (46)
Female	165 (54)
Race	
White	239 (78)
Other	5 (2)
Unknown	63 (21)
Type of myotonic dystrophy	
1	118 (38)
2	86 (28)
Unknown	103 (34)
Diagnosis with electromyography	
Yes	123 (40)
No	1 (<1)
Unknown	183 (60)
Genetic testing	
Yes	165 (54)
No	19 (6)
Unknown	123 (40)
Cancer diagnosis	
At least 1	41 (13)
Never	266 (87)
Age at last contact (y), mean (SD)	49.3 (16.7)
Age at symptom presentation (y), mean (SD)	39.6 (15.0)
Age at diagnosis for affected patients (y), mean (SD)	54.7 (13.2)

We observed a total of 53 cancers in 41 patients with myotonic dystrophy (15 type 1, 18 type 2, 8 unknown type) at a median age at diagnosis of 55 years (mean ± SD age, 54.7±13.2 years). Table 3 shows that a total of 5 thyroid cancers (3 papillary carcinomas, 1 medullary carcinoma, and 1 unknown for histology) were observed at median age at diagnosis of 42 years; this was an approximately 6-fold increased risk compared with the general population (SIR, 5.54; 95% CI, 1.80-12.93; P=.001). Two cases of thyroid cancer were observed in patients with type 1 myotonic dystrophy and 2 cases in patients with type 2; in the other case, the type of myotonic dystrophy was unknown (Table 4).

We observed 2 cases of choroidal melanoma, both of which were diagnosed at age 44 years and in patients with myotonic dystrophy type 1, which was an approximately 28-fold higher risk than expected for the general population (SIR, 27.54; 95% CI, 3.34-99.49; P<.001) (Table 3).

The estimated cumulative risks for thyroid cancer were 1.72% (95% CI, 0.64%-4.55%) at age 50 years and 3.53% (95% CI, 1.50%-8.18%) at age 70 years. The estimated cumulative risk for choroidal melanoma was 1.00% (95% CI, 0.25%-3.92%) at age 50 years.

The incidence of testicular and prostate cancers was increased but did not reach statistical significance: testicular cancer SIR, 5.09, 95% CI, 0.62-18.38, P=.06; and prostate cancer SIR, 2.21, 95% CI, 0.95-4.35, P=.05. We also observed 9 nonmelanoma skin cancers (8 basal cell carcinomas and 1 squamous cell carcinoma) at median age at diagnosis of 57 years. Because there are no referent incidences of nonmelanoma skin cancers for the general population (eg, SEER data), we are unable to estimate SIR to state whether this is excessive. Of the nonmelanoma skin cancers, 3 were observed in patients with myotonic dystrophy type 1 and 6 in patients with type 2. There was no statistical evidence of an increased risk of brain, breast, colorectal, lung, renal, bladder, endometrial, or ovarian cancers; lymphoma; leukemia; or multiple myeloma (Table 3).

DISCUSSION

In this analysis of medical records of 307 individuals with myotonic dystrophy seen one or more times as patients at Mayo Clinic, we have demonstrated an increased risk of thyroid cancer and choroidal melanoma compared with the incidence of these tumors in the US general population. There was also a suggestion of increased risks for cancers of the prostate and testicles, although this did not reach statistical significance.

The association with an increased risk of thyroid cancer is novel and convincing. Endocrine dysfunction in myotonic dystrophy is known to commonly involve insulin insensitivity and primary gonadal failure in males, but the literature on thyroid problems in myotonic dystrophy is limited. In their review of all neoplasms reported in the literature in conjunction with myotonic dystrophy of both types, Mueller et al[17] encountered instances of colloid goiter, thyroid adenoma, medullary thyroid cancer, and thyroid cancers (type unknown) but were unable to state whether these observations exceed what is expected in such a population. Daumerie et al[19] reported studying the CTG repeat number in a benign thyroid nodule in a patient with type 1 myotonic dystrophy and found that the triplet expansion was 7 times larger than the expansion found in lymphocytes. Fukazawa et al[20] investigated 12 patients with myotonic dystrophy for endocrine disturbances. All were euthyroid, but the free triiodothyronine level was somewhat lower than in controls, the mean maximal thyrotropin response was less than in controls, and radioiodine uptake was decreased. An earlier report by Steinbeck and

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TABLE 3. Standardized Incidence Ratios and Their 95% Confidence Intervals for Cancers in Patients With Myotonic Dystrophy (Type 1, Type 2, and Unknown Combined) Compared With the General Population[a]

Cancer	Age (range) at diagnosis of cancer, y[b]	O	E	SIR	95% CI	*P* value
Both sexes						
Choroidal melanoma	44 (44-44)	2	0.07	27.54	3.34-99.49	<.001
Thyroid	42 (13-58)	5	0.90	5.54	1.80-12.93	.001
Multiple myeloma	59	1	0.31	3.19	0.08-17.79	.40
Lymphoma	54 (36-77)	4	1.66	2.41	0.66-6.17	.12
Kidney	58 (53-63)	2	0.84	2.39	0.29-8.64	.30
Leukemia	63 (50-76)	2	0.91	2.19	0.27-7.91	.36
Melanoma	47 (44-60)	3	1.46	2.05	0.42-6.00	.29
Brain	46	1	0.65	1.54	0.04-8.57	.75
Colorectum	58 (44-62)	3	2.76	1.09	0.22-3.18	.90
Urinary bladder	65	1	0.93	1.07	0.03-5.98	.96
Breast	62 (43-65)	5	5.25	0.95	0.31-2.22	.92
Lung	54 (50-80)	3	3.48	0.86	0.18-2.52	.82
Nonmelanoma skin[c]	57 (42-80)	9	NA[d]	NA	NA	
Female						
Ovary	60	1	0.60	1.66	0.04-9.25	.72
Endometrium	30	1	0.93	1.07	0.03-5.98	.82
Male						
Testis	42 (36-47)	2	0.39	5.09	0.62-18.38	.06
Prostate	62 (45-69)	8	3.62	2.21	0.95-4.35	.05

[a] BCC = basal cell carcinoma; CI = confidence interval; E = expected number of cancers; NA = not applicable; O = observed number of cancers; SIR = standardized incidence ratio.

[b] Median age at diagnosis (minimum-maximum range) for cases that were observed more than once.

[c] Nonmelanoma skin cancers included BCC, unspecified location (n=5); BCC, lips (n=1); BCC, left nasal dorsum (n=1); BCC, face (n=1); and squamous cell carcinoma, unspecified location (n=1).

[d] There are no available population incidences from which to calculate SIR for nonmelanoma skin cancers. These data are not collected by Surveillance, Epidemiology, and End Results registries.

Carter[21] stated that 15% of their series of 20 young adults with myotonic dystrophy and 20% of cases described (20/102) before their report had palpable thyroid abnormalities. They also showed reduced thyrotropin response to thyrotropin-releasing hormone, despite euthyroid status as judged by circulating thyroid hormone level. Our study is the first to document statistically increased risks for thyroid cancers (papillary, medullary, and 1 unknown type), with estimated disease penetrance of about 4% by age 70 years. Careful annual palpation of the thyroid gland is indicated for adults with myotonic

TABLE 4. Standardized Incidence Ratios and Their 95% Confidence Intervals for Patients With Myotonic Dystrophy Type 1, Type 2, and Unknown Type

	Type 1				Type 2				Unknown type			
Cancer	O	E	SIR (95% CI)	*P* value	O	E	SIR (95% CI)	*P* value	O	E	SIR (95% CI)	*P* value
Thyroid	2	0.27	7.40 (0.90-26.71)	.02	2	0.35	5.70 (0.69-20.59)	.05	1	0.28	3.56 (0.09-19.84)	.36
Choroidal melanoma	2	0.02	92.94 (11.26-335.72)	<.001	0				0			
Testis	1	0.12	8.27 (0.21-46.08)	.12	0				1	0.15	6.61 (0.17-36.84)	.17
Prostate	1	0.87	1.15 (0.03-6.43)	.37	6	1.79	3.36 (1.23-7.32)	.008	1	0.97	1.03 (0.03-5.73)	.98

CI = confidence interval; E = expected number of cancers; O = observed number of cancers; SIR = standardized incidence ratio.

dystrophy, and imaging should be offered to those with any palpable abnormalities.

Choroidal melanomas were reported in this study, but because only 2 cases were observed, the CIs are wide and further validation of this observation will be important. We recommend that patients with myotonic dystrophy be offered an ophthalmologic evaluation annually in adulthood because of the known high incidence of cataracts in both type 1 and type 2 myotonic dystrophy, as well as this new possible association with choroidal melanoma.

We observed marginal evidence of increased risk for testicular cancer and prostate cancer, but further studies are needed to determine whether this result is of any significance. It is unclear how an increased risk for testicular cancer may be related to the well-documented risk for male infertility and hypogonadism in myotonic dystrophy, but one could speculate that there is a connection. In the meanwhile, health care providers for men with myotonic dystrophy may want to make a point of examining testicles annually and to implement prostate cancer screening by age 50 years.

In this study, we observed brain, breast, colorectal, lung, renal, bladder, endometrial, and ovarian cancers; cutaneous melanoma; lymphoma; leukemia; and multiple myeloma in patients with myotonic dystrophy. These cancers have also been reported in previous clinical and case reports. However, we did not observe statistical evidence of an increased risk of these cancers. Several studies have reported benign neoplasms observed in patients with myotonic dystrophy, especially pilomatricomas[22,23] and thymoma,[24-29] but data on benign neoplasms were not available in our patients with myotonic dystrophy to quantify their risks.

Genetic mechanisms and underlying pathophysiology responsible for tumorigenesis in patients with myotonic dystrophy are not known. The CTG expansion in *DMPK* and the CCTG expansion in *CNBP* both occur in the noncoding portions of these genes: they are transcribed but apparently do not affect the protein-coding regions of those genes. The altered RNA is sequestered in the nucleus and has been documented to alter normal function of RNA splicing factors, which likely affect a large number of downstream targets. Research suggests that "the basic molecular mechanism is disruption of messenger RNA metabolism, which has far-reaching effects on many other genes."[30] On the basis of clinical and in vitro evidence, Mueller et al[17] developed a hypothesis regarding predisposition to neoplasms and for tumor progression in myotonic dystrophy that invokes the up-regulation of β-catenin via the *Wnt* signaling pathway and possibly via the actions of RNA splicing factors (eg, CUG-BP1, MBNL, and likely many others) that could affect many downstream genes. At present, it is safe to say that the mechanisms of dysfunction wrought by the disease-causing trinucleotide and tetranucleotide expansions in *DMPK* and *CNBP* are very poorly understood but merit further research.

This study was based on 53 cancers observed in a retrospective cohort of 307 patients with myotonic dystrophy. To our knowledge, it is the largest sample to date used to investigate cancer risks for patients with myotonic dystrophy and the first to attempt quantification of risks. This study had notable limitations: it was a retrospective chart review; the number of cases is too small to address more definitively many of the site-specific cancer risks; one-third of the cases could not be classified as type 1 or type 2 myotonic dystrophy; how many different families are represented by the 307 cases is unclear; environmental risk exposure histories on the cases are not available; and some cancers were self-reported.

We considered whether our ascertainment of the included patients may have skewed our results in some way. Of the 5 patients with thyroid cancer, only 1 was referred specifically for the expertise offered at Mayo Clinic for thyroid cancer. The others were diagnosed with cancer years before or after coming to Mayo Clinic. The 2 patients with choroidal melanoma were both referred to the Ophthalmology Department at Mayo Clinic because of their choroidal lesions and therefore may not be fully representative of patients with myotonic dystrophy in the community setting. However, we did not ascertain myotonic dystrophy on the basis of a diagnosis of cancer or a family history of cancer, and therefore the estimates from this study are less likely to be inflated because of ascertainment bias.[31] We fully acknowledge how ideal it would be to have a larger population-based case series with prospectively collected data.

CONCLUSION

Patients with myotonic dystrophy may have an increased risk of thyroid cancer and choroidal melanoma and may also have an increased risk of prostate and testicular cancers. Perhaps this study will prompt development of a properly designed multicenter study that can capture this information prospectively on a larger number of cases of myotonic dystrophy.

ADDENDUM

After completing our research, and after our manuscript was accepted for publication in this journal, we learned that Gadalla et al[32] have also reported an association between myotonic muscular dystrophy and cancer risks. Their multinational study was larger (1658 patients) and—in addition to reporting an association with thyroid cancer—differed from

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ours in identifying increased risks for cancers of the endometrium, brain, ovary, and colon. One of the inclusion criteria for their study was having a diagnosis of myotonic muscular dystrophy but types 1, 2, and other were combined. The SIR for thyroid cancer in their study was 7.1 (95%CI 1.8-19.3) with a *P* value of 0.01. The independent reporting of the association of myotonic muscular dystrophy with increased cancer risks by now 2 separate research groups lends credibility to the discoveries.

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