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Cancer Risk among Patients with Myotonic Muscular Dystrophy

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Abstract

Context—Myotonic muscular dystrophy (MMD) is an autosomal dominant multisystem neuromuscular disorder characterized by unstable nucleotide repeat expansions. Case reports have suggested that MMD patients may be at increased risk of malignancy, putative risks which have never been quantified.

Objective—To quantitatively evaluate cancer risk in patients with MMD, overall, and by sex and age.

Design, Setting, and Participants—We identified 1,658 patients with an MMD discharge diagnosis in the Swedish Inpatient Hospital or Danish Patient Discharge Registries between 1977 and 2008. We linked these patients to their corresponding cancer registry. Patients were followed from date of first MMD-related inpatient or outpatient contact, to first cancer diagnosis, death, emigration, or completion of cancer registration.

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Conflict of interest: None

Main Outcome Measures—Risks of all cancers combined, and by anatomic site, stratified by sex and age.

Results—104 patients with an inpatient or outpatient discharge diagnosis of MMD developed cancer during post-discharge follow-up. This corresponds to an observed cancer rate of 73.4/10,000 person-years in MMD *versus* an expected rate of 36.9/10,000 in the general Swedish and Danish populations combined (SIR =2.0, 95% CI =1.6–2.4). Specifically, we observed significant excess risks of cancers of the endometrium (observed rate=16.1/10,000 person-years: SIR=7.6, 95%CI=4.0–13.2), brain (observed rate=4.9/10,000 person-years: SIR=5.3, 95%CI=2.3–10.4), ovary (observed rate=10.3/10,000 person-years: SIR=5.2, 95% CI=2.3–10.2), and colon (observed rate=7.1/10,000 person-years: SIR=2.9, 95%CI=1.5–5.1). Cancer risks were similar in females and males after excluding genital organ tumors (SIR=1.9, 95% CI=1.4–2.5 vs. 1.8, 95% CI=1.3–2.5, respectively, p-heterogeneity=0.81; observed rates=64.5 and 47.7/10,000 person-years in women and men, respectively). The same pattern of cancer excess was observed first in the Swedish, and then in the Danish cohorts, which were studied sequentially and initially analyzed independently.

Conclusions—MMD patients identified from the Swedish and Danish patient registries were at increased risk of cancer both overall and for selected anatomic sites.

Keywords

Myotonic dystrophy; genomic instability; cancer risk

Introduction

Myotonic Muscular Dystrophy (MMD) - is an autosomal dominant, multi-system disorder comprised of two subtypes¹. MMD type 1 (MMD1; MIM # 160900) is caused by unstable trinucleotide (CTG) repeat expansion in the 3' untranslated region of the dystrophin myotonia-protein kinase (*DMPK*) gene^{2–4}; type 2 (MMD2; MIM # 602668) is a tetra-nucleotide (CCTG) repeat expansion in intron 1 of the zinc finger 9 (*ZNF9*) gene^{5,6}. It is the most common adult muscle dystrophy, with an estimated prevalence ranging between 0.5–18/100,000⁷. MMD1 displays a more severe phenotype that can present at any age (median=20–30 years)¹, and result in premature death (at 50–65 years of age)^{8,9}. Both subtypes share myotonia and progressive skeletal muscle weakness and wasting. Other manifestations include cardiac conduction defects, insulin-resistance, testicular atrophy, respiratory insufficiency, cognitive impairment, and premature cataract¹. Both MMD subtypes result from interactions between CUG or CCUG repeat RNA and regulatory binding proteins, mainly the muscle-blind-like (MBNL) protein family¹⁰, which lead to abnormal regulation of pre-mRNA alternative splicing¹¹. MBNL1 depletion in MMD has been implicated in the development of myotonia, pre-mature cataract¹² and skin cancer^{13,14}.

Case reports have suggested that MMD patients may be at increased risk of benign and malignant tumors. Pilomatricoma, a rare benign calcifying cutaneous neoplasm derived from hair matrix cells, is the most commonly reported. Additionally, multiple skin basal cell carcinomas have been suggested as an MMD phenotypic variant^{14–17}. We have previously reviewed this literature, described neoplasms reported by subjects enrolled in the National Registry of MMD and Facioscapulohumeral Muscular Dystrophy and Family Members, and discussed possible molecular reasons for a hypothetical cancer predisposition¹³.

To further explore whether the MMD phenotype includes cancer risk, we conducted a population-based linkage study of MMD patients using the nationwide Swedish and Danish

registries. Our data comprise the first objective, quantitative evidence to suggest that the MMD syndrome includes cancer susceptibility.

Methods

Myotonic Muscular Dystrophy - Swedish Cohort

Within the Swedish Inpatient Hospital Discharge Registry, which began in 1964 and reached 100% nationwide hospitalization coverage in 1987, we identified all patients with an MMD discharge diagnosis (ICD-9=359C; ICD-10=G711) between January 1987 and December 2004 (n=768). Diagnoses were coded using the International Classification of Diseases (ICD) Revision 7: 1964–1968; Revision 8: 1969–1986; Revision 9: 1987–1995; and Revision 10 thereafter^{18,19}. We excluded 99 patients from analysis: 59 had cancer prior to, or at the time of, MMD first hospitalization; 36 died during first hospitalization; and 4 had incomplete data. Using the Swedish national identification number, MMD patients were linked to the Cancer Registry. The Swedish MMD cohort did not capture patients who were managed exclusively as outpatients. When analyses in Swedish MMD patients suggested a possible excess cancer risk, we sought to replicate our findings in a separate, independent population (Danish cohort).

Myotonic Dystrophy - Danish Cohort

The Danish Patient Registry covers all hospital admissions and outpatient visits since 1977, and 1995, respectively. All Danish Registry diagnoses are coded according to ICD Revision 8: 1969–1993; and Revision 10 from 1994 onwards²⁰. Each individual's unique civil registration number was used to link the patients to the Danish Cancer Registry. After excluding registrants with prior cancer, or who died prior to follow-up initiation, we identified 989 inpatients or outpatients discharged with an MMD diagnosis between 1977 and 2008 (ICD-8=330.90, 330.91; ICD-10=G711). See Figure 1 for a flow chart of each country's participant selection and subject number.

Cancer Ascertainment

The Swedish and Danish Cancer Registries have identified all incident cancers detected in Sweden and Denmark since 1958, and 1943, respectively. Registries completeness and diagnostic accuracy exceeded 95% in several validation studies^{21–24}. For this study, cancer sites were identified using the ICD-7 and ICD-10 codes from Sweden, and Denmark, respectively. To ensure comparability between reported cancer sites, we used a slightly modified version of the NORDCAN cancer dictionary²⁵, which was initiated by the Association of the Nordic Cancer Registries (ANCR) and the International Agency for Research on Cancer (IARC) to formalize Nordic countries' data harmonization.

Amendments to the cancer codes were made for cancers of the brain (only malignant tumors were included), as well as lymphoma and leukaemia, to accommodate differing coding schemes over time in Denmark and Sweden, respectively. Furthermore, we included sub-analyses of rectum and anal cancers in recognition of their etiologic differences. Non-melanoma skin cancers were not considered in the current analyses due to differing registration practices between the two countries²⁴.

Ethical Approval and Informed Consent

Access to the Swedish and Danish registries' data was approved by the Karolinska Institutional Review Board, Sweden, and the Danish Data Protection Agency, respectively. Informed consent was waived because we had no contact with study subjects. An institutional review board waiver was obtained from the NIH Office of Human Subjects Research because all analyses were performed using de-identified data.

Statistical Analysis

We calculated standardized incidence ratios (SIRs) (observed cancers in MMD patients, divided by expected number of cancers) for all cancers combined, and by anatomic site, stratified by gender and age (< 50 and ≥ 50 years). Expected cancer numbers were calculated by applying country-, age-, gender-, and calendar-time specific population incidence rates from each cancer registry to the person-years observed among its subset of MMD cases. To avoid survival bias affecting cancer risk estimates, MMD patients were followed-up from date of first MMD-related inpatient discharge diagnosis, or date of first outpatient contact, to the first cancer diagnosis, death, emigration, or the end of complete cancer registration (Sweden: December 31, 2004; Denmark: December 31, 2008). The observed and expected cancer rates for MMD patients were calculated by dividing the observed and expected numbers of cancers by the person-years of follow-up.

In a subgroup analysis using the Danish database, we calculated SIRs for all cancers combined, stratified by type of hospital contact (inpatient *vs.* outpatient), as a proxy of disease severity, hypothesizing that patients who were hospitalized represented a more severe MMD phenotype. Patients first identified from the outpatient registry and who were hospitalized subsequently (n=125) contributed person-years of follow-up to the outpatient group until first hospitalization date, and to the inpatient group subsequently. Of note, 331(72.6%) of 456 Danish MMD patients first ascertained in the outpatient setting were never hospitalized during follow-up.

We evaluated the risk of each cancer site, and considered an association to be statistically significant at a level of $p=0.05$. In the Results and Comment, we focused primarily on associations with p -values less than 0.01, to minimize multiple testing-related false discovery. Mid- p tests and confidence intervals, defined by the mean value of the Poisson distribution that makes the probability that the test statistic is less than its observed value plus half the probability of its observed value equal to 0.975 (upper limit) and 0.025 (lower limit)²⁶, were used throughout. Subgroup interactions were tested using conditional exact tests with mid- p values. Since the site-specific SIRs were not to differ statistically in the two national cohorts, the data were combined for presentation (see eTable 1) for country-specific data.

Results

The study included 1,658 MMD patients (Sweden=669; Denmark=989), contributing 4,724 and 9,446 person-years of observation, respectively. In Sweden, the patients' median age at first MMD discharge diagnosis (inpatient only) was 46 years, *versus* 38 years in Denmark (41 years for inpatients and 37 years for outpatients). In both countries, approximately half were males, 40% died during follow-up, and 6 % developed cancer (Table 1).

During 14,170 person-years of follow-up, 104 MMD patients developed cancer compared with 52.3 expected cases, corresponding to an observed cancer rate of 73.4/10,000 person-year in MMD patients *versus* an expected rate of 36.9/10,000 person-years. Compared with expected case numbers based on cancer rates in the general population, MMD patients had an increased overall cancer risk (SIR=2.0, 95% CI=1.6–2.4). Most notably, we observed significant excesses of endometrial (observed rate=16.1/10,000 person-years; SIR=7.6, 95% CI=4.0–13.2), brain (observed rate=4.9/10,000 person-years; SIR=5.3, 95% CI=2.3–10.4), ovarian (observed rate=10.3/10,000 person-years; SIR=5.2, 95% CI=2.3–10.2), and colon cancers (observed rate=7.1/10,000 person-years; SIR=2.9, 95% CI=1.5–5.1). Our data also suggested possible excesses of eye (observed rate=1.4/10,000 person-years; SIR=12.0, 95% CI=2.0–39.6), other female genital organs (observed rate=2.9/10,000 person-years; SIR=9.6, 95% CI=1.6–31.8), thyroid (observed rate=2.1/10,000 person-years; SIR=7.1, 95% CI=1.8–

19.3), and pancreas cancers (observed rate=2.8/10,000 person-years; SIR=3.2, 95% CI=1.0–7.6); (Table 2). Close similarity in overall and site-specific cancer excess was observed in both the Swedish and Danish MMD patients (eTable 1).

After excluding genital organ cancers (uterus, cervix, ovary and fallopian tubes, vulva, vagina, prostate, testis, penis, scrotum, and unspecified parts), no statistically significant gender difference was observed in overall cancer risk (SIR=1.9, 95% CI=1.4–2.5 in women vs. 1.8, 95% CI=1.3–2.5 in men, p-heterogeneity=0.81: observed rates=64.5 and 47.7/10,000 person-years in women and men, respectively). However, the data suggested possible gender-specific differences for cancers of the rectum and lung (Table 3), findings that did not reach statistical significance.

In age-stratified analyses (<50 vs. ≥50 years), no statistically significant difference was observed in overall cancer risk (SIR=2.2, 95% CI=1.4–3.2 and 1.9, 95% CI=1.6–2.4, respectively, p-heterogeneity=0.58: observed rates=25.7 and 165.6/10,000 person-years in the younger and older age group, respectively). However, we did observe a significantly higher excess risk of early-onset endometrial cancer among women aged <50 years (observed rate=11.1/10,000 person-years: SIR=35.6, 95% CI=13.0–78.9) versus women aged ≥50 years (observed rate=25.8/10,000 person-years: SIR=4.6, 95% CI=1.9–9.5, p-heterogeneity=0.003). Also, our data suggested a higher risk of early-onset lung (p-heterogeneity=0.08), and esophageal cancer (p-heterogeneity=0.01) (Table 4).

In a subgroup analysis among Danish patients by type of hospital contact, our data suggested that inpatients were at higher risk of developing cancers than outpatients the difference, however, did not reach statistical significance (SIR=2.0, 95% CI=1.5–2.6, vs. 1.1, 0.5–2.0, respectively, p-heterogeneity=0.08).

In three additional analyses based on the Danish cohort, we found the overall results to remain the same when starting follow-up 5 years after the first MMD discharge diagnosis (SIR=2.04, 95% CI=1.49–2.72), when restricting the analysis to those with MMD as their main diagnosis (SIR=1.8, 95% CI=1.4–2.4), and to those inpatients with no diagnoses other than MMD at the first MMD admittance (n=255) (SIR=1.9, 95% CI=1.3–2.8). Among the 287 MMD patients who had main discharge diagnosis other than MMD, family history of congenital/specified condition (n=34) was the most commonly reported, followed by respiratory (n=33, 33% of whom had respiratory failure), cardiovascular (n=27), and eye diseases (n=22, 55% of whom had cataract).

Comment

Our study is the first to quantify cancer risk in patients with MMD. In this large population-based study, we observed an excess cancer risk compared with the general population, first among Swedish MMD patients, and then among the replication cohort of Danish patients. Due to the close similarity in the results and to improve statistical power, we combined the findings from these two cohorts. The elevated overall cancer risk was primarily due to excess malignancies of the endometrium, brain, ovary, and colon.

Case reports have suggested a strong association between MMD and pilomatricoma, a rare benign skin neoplasm (which is not registered in the Swedish Cancer Registry and incompletely registered in the Danish Cancer Registry) and also included reports of a number of rare malignancies¹³. Published case reports tend to present a biased sample of unusual cases, and therefore cannot provide conclusive evidence of a genuine association. This methodological shortcoming led to the current study, which provides strong evidence that MMD may in fact be a cancer susceptibility disorder.

Several biological mechanisms for the apparent increased cancer risk have been proposed including possible RNA-mediated alterations in tumor suppressor genes or oncogene expression, modification of the coding features of proteins²⁷, and/or up-regulation of the *Wnt/β-catenin* signaling pathway¹³. Of note, alteration in RNA binding proteins, suggested as a key player in MMD pathogenesis, have been observed in human carcinogenesis²⁸. On the other hand, it is worth noting that the *DM1* gene product – DMPK (MIM #605377) – is a protein kinase, *i.e.*, a member of a large gene family which contains numerous examples of cancer susceptibility genes, such as *RET* (MEN2), *STK11* (Peutz-Jeghers syndrome), *PRKARIA* (Carney complex), *RAF1* (Noonan syndrome), *ALK* (neuroblastoma) and *PDGFRA* (GIST)²⁹.

The absence of an excess cancer risk in other repeat disorders, *e.g.*, fragile-X³⁰ and Huntington disease³¹ is noteworthy. It is possible that repeat expansion size may be a key determinant of cancer risk in this context, since nucleotide repeat expansions are much longer in MMD patients compared with Huntington disease or fragile-X patients³², and several case reports have demonstrated longer nucleotide repeat expansion in tumor tissue from MMD patients compared with their normal tissue^{33;34}. If proven true, we would expect that patients with MMD2, who are known to have the longest repeat sizes, would have higher risk of cancer, a hypothesis that needs further investigation. The observed cancer risk differences between various repeat disorders might also be related to the precise repeat expansion location within the affected gene. MMD differs from Huntington disease by having expansion in a non-coding region, which is more likely to produce a toxic RNA mediated gain-of-function that can affect downstream effector genes^{5;35}, some of which maybe tumor suppressor genes, *e.g.*, mismatch repair genes (MMR). Additional analyses of paired normal tissue and tumor samples from well-characterized MMD patients could shed further light on the relationship between expansion repeat length and cancer risk in MMD.

Surprisingly, the cancer spectrum we observed in MMD patients included many of the same excess cancers observed in patients with hereditary non-polyposis colorectal cancer (HNPCC)³⁶, *e.g.*, colon, brain, ovary and endometrium. In that context, MMD-related pilomatricoma may be analogous to the increased risk of sebaceous adenoma in the Muir-Torre variant of HNPCC. Inherited DNA mismatch repair (MMR) abnormalities are the genetic basis for HNPCC, a prototypic cancer susceptibility disorder³⁶. Defective MMR may play a role in the formation of unstable nucleotide repeats, perhaps through a disease-specific mechanism^{37;38}. The nexus between the nucleotide repeat expansion pathway and MMR warrants further investigation in this context, because *in vitro* studies³⁸ and mouse models^{39–41} suggest that abnormal MMR plays a major role in mediating the biological effects of MMD-related nucleotide repeat instability. eTable 2 summarizes the observed cancer profile in MMD patients *versus* HNPCC patients. The occurrence of a similar spectrum of malignancies in both raises the possibility of shared causal pathways.

Our study has several strengths. We used population-based registries, minimizing selection bias and maximizing complete cancer ascertainment. Both MMD and cancer diagnoses were derived from registry-based records, rather than self-report, minimizing recall bias. The study included MMD patients identified from both inpatient and outpatient registries, broadening the generalizability of our results. However, the severely-affected MMD subset is still likely to be over-represented, since the majority of patients in the study were identified from inpatient hospitalization records. The remarkable similarity of findings obtained from the Swedish and Danish components of the study provides substantial reassurance that our observations are genuine. The absence of excess screening-related cancers such as breast, cervical, and prostate in our analysis argues against a possible influence of surveillance bias on our results. Most of the excess cancers observed in the present study were lethal cancers that would be diagnosed regardless of whether a person

had prior contact with the health care system. Thus, surveillance bias did not appear to influence our results. Furthermore, we found MMD patients with a similarly increased risk of cancer when restricting the analyses to more than five years after first MMD discharge diagnosis, to those with MMD as main diagnosis, and to those with no other diagnoses besides MMD at the first MMD admittance, arguing against the possibility that our results may be confounded by cause of hospitalization or increased surveillance.

Due to the under-reporting of non-melanoma skin cancer in the Swedish cancer registry, we were not able to fully evaluate its risk in MMD. However, data available from the Danish registry only, suggested a possible excess risk of non-melanoma skin cancer (SIR= 2.08, 95% CI=1.2–3.4), an association that needs further confirmation. Of note, our combined data suggested an excess risk of cutaneous melanoma, although not statistically significant.

The lack of information regarding known cancer risk factors, *e.g.*, smoking, which prevented evaluating them as possible confounders, represents one important study limitation. In addition, our data did not permit identifying which specific MMD subtype each subject had, so we could not determine if the increased cancer risk observed in MMD was common to all patients or confined to a specific subtype. We expect that most of the cases in this study were MMD1, because it is more prevalent, and it was identified and molecularly-characterized before MMD 2. Furthermore, we did not have data on gene repeat length. Thus, it remains to be evaluated in future studies to what extent gene repeat length modifies the cancer risk. Finally, we acknowledge that the point estimates for some of the cancer sites had wide confidence intervals, which make firm conclusions for these sites less reliable.

In conclusion, our study provides quantitative epidemiologic evidence of an increased risk of cancer in MMD patients. The specific cancer patterns observed in our study raise the possibility of a role for aberrant mismatch repair in the etiology of MMD-related cancer. Further research is needed to explore whether the observed associations are similar in both MMD1 and 2, to determine whether cancer risk correlates with disease severity and/or repeat length, and to understand the biological mechanisms which might explain the associations we have reported. Our findings have significant implications for the clinical management of MMD patients, including at a minimum the implementation of appropriate validated routine population-based cancer screening strategies, and careful assessment of therapy-related risks and benefits. The incidence rates for a number of the excess cancers are relatively low, despite their large relative risks. Screening for these uncommon cancers should not be implemented in the absence of demonstrated clinical utility. The evaluation of persistent CNS and abdominopelvic symptoms or dysfunctional uterine bleeding warrants clinical consideration with a higher prior probability of neoplasm, in light of our new findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Flow chart describing the selection of Swedish and Danish DM patients for inclusion in the current study

Table 1

Characteristics of the Swedish and Danish Myotonic Dystrophy (DM) Cohorts

Variable	Sweden N=669	Denmark N=989
N (%)		
Gender		
Male	331 (49.5)	530 (53.6)
Female	338 (50.5)	459 (46.4)
Age at first DM discharge diagnosis		
<i>Median (range) (Yrs)</i>	<i>46 (0–86)</i>	<i>38 (0–85)</i>
0–14 years	71 (10.6)	130 (13.1)
15–29 years	86 (12.9)	188 (19.0)
30–44 years	168 (25.1)	304 (30.7)
45–59 years	244 (36.5)	267 (27.0)
≥ 60 years	100 (14.9)	100 (10.1)
Calendar Year at first DM discharge diagnosis		
1977–1981	0	156 (15.8)
1982–1986	0	112 (11.3)
1987–1991	261 (39.0)	96 (9.7)
1992–1996	171 (25.6)	143 (14.5)
1997–2001	157 (23.5)	196 (19.8)
2002–2006 [^]	80 (12.0)	204 (20.6)
2007–2008	0	82 (8.3)
Had cancer during follow-up	43 (6.4)	61 (6.2)
<i>Age Yrs: Median (range)</i>	<i>57 (24–85)</i>	<i>56 (27–87)</i>
Died during follow up	255 (38.1)	387 (39.1)
<i>Age Yrs: Median (range)</i>	<i>59 (0–89)</i>	<i>58 (0–93)</i>

[^] Up to 2004 for the Swedish data.

Table 2

Standardized incidence ratios (SIR) of cancers in Swedish and Danish patients with myotonic dystrophy by anatomic site

Anatomic site [^]	Person-Year=14,170		SIR (95% CI)	P-value
	N	Expected		
All sites except non-melanoma skin	104	52.28	2.0 (1.6–2.4)	<0.00001
Pharynx	1	0.55	1.8 (0.1–9.1)	0.52
Esophagus	2	0.59	3.4 (0.6–11.2)	0.14
Colon	10	3.47	2.9 (1.5–5.1)	0.004
Rectum and anus	5	2.47	2.0 (0.7–4.5)	0.15
Rectum	5	2.30	2.2 (0.8–4.8)	0.11
Anus	0	0.17	0	
Liver	2	0.48	4.2 (0.7–13.8)	0.10
Pancreas	4	1.27	3.2 (1.0–7.6)	0.05
Nose, sinuses	1	0.11	9.0 (0.5–44.4)	0.11
Lung	10	5.98	1.7 (0.8–3.0)	0.12
Melanoma (skin)	6	2.58	2.3 (0.9–4.8)	0.06
Breast	11	9.40	1.2 (0.6–2.0)	0.58
Cervix	1	1.15	0.9 (0.0–4.3)	0.99
Endometrium	11	1.45	7.6 (4.0–13.2)	<0.00001
Ovary, tube, broad ligament	7	1.36	5.2 (2.3–10.2)	0.0006
Other female genital organs	2	0.21	9.6 (1.6–31.8)	0.02
Prostate	3	4.20	0.7 (0.2–1.9)	0.61
Testis	1	0.73	1.4 (0.1–6.8)	0.68
Kidney	2	1.21	1.7 (0.3–5.5)	0.46
Other Urinary organs	1	2.62	0.4 (0.0–1.9)	0.34
Eye [*]	2	0.17	12.0 (2.0–39.6)	0.01
Central Nervous System	7	1.60	4.4 (1.9–8.7)	0.002
Brain [‡]	7	1.33	5.3 (2.3–10.4)	0.0005
Thyroid gland	3	0.42	7.1 (1.8–19.3)	0.01
Acute Leukemia	1	0.50	2.0 (0.1–9.8)	0.49

Anatomic site [^]	Person-Year=14,170		SIR (95% CI)	P-value
	N	Expected		
Non-Hodgkin lymphoma	3	1.67	1.8 (0.5–4.9)	0.32
Other sites [†]	8	2.56	3.1 (1.4–5.9)	0.006

[^] Sites with no cases: lip, tongue, mouth, salivary glands, stomach, small intestine, gallbladder, larynx, pleura, bone, soft tissues, other parts of the uterus, male genital organs, Hodgkin Lymphoma, multiple myeloma, and chronic leukemia

^{*} One case was mixed epitheloid spindle cell melanoma, and the second was malignant but unknown histology

[‡] 3 cases were astrocytoma, 1 glioblastoma, 1 astroblastoma, 1 oligodendroglioma, 1 malignant but unknown histology

[†] Other sites include cancers of the parathyroid (n=2), other unspecific/unknown primary site (n=5), and neoplasm of the retroperitoneum (n=1)

Table 3

Standardized incidence ratios (SIR) of cancers in Swedish and Danish patients with myotonic dystrophy by selected[^] anatomic sites and gender

Anatomic site	Male N=861; person-years=7,345			Female N=797; person-years=6,825			P-heterogeneity
	N	Expected	SIR (95% CI)	N	Expected	SIR (95% CI)	
All sites, except non-melanoma skin	39	24.72	1.6 (1.1–2.1)	65	27.55	2.4 (1.8–3.0)	0.05
All sites, except genital organs	35	19.69	1.8 (1.3–2.5)	44	23.3	1.9 (1.4–2.5)	0.81
Colon	5	1.75	2.9 (1.0–6.3)	5	1.72	2.9 (1.1–6.4)	0.98
Rectum	1	1.40	0.7 (0.0–3.5)	4	0.90	4.4 (1.4–10.7)	0.09
Pancreas	3	0.68	4.4 (1.1–12.0)	1	0.59	1.7 (0.1–8.4)	0.45
Lung	9	3.61	2.5 (1.2–4.6)	1	2.42	0.4 (0.0–2.0)	0.05
Central Nervous System	4	0.85	4.7 (1.5–11.4)	3	0.75	4.0 (1.0–10.9)	0.85
Brain	5	0.71	5.6 (1.8–13.5)	3	0.62	4.9 (1.2–13.2)	0.87
Eye	1	0.09	11.0 (0.6–54.4)	1	0.08	13.1 (0.7–64.8)	0.91
Thyroid gland	0	0.12	0	3	0.30	9.8 (2.5–26.8)	0.37
Endometrium		N/A		11	1.45	7.6 (4.0–13.2)	
Other female genital organs		N/A		2	0.21	9.6 (1.6–31.8)	
Ovary, tube and broad ligament		N/A		7	1.36	5.2 (2.3–10.2)	

[^] Anatomic sites presented in this table are those with a statistical significant excess risk overall, or sites with gender-specific risk

Standardized incidence ratios (SIR) of cancers in Swedish and Danish patients with myotonic dystrophy before and after 50 years of age by selected^a anatomic sites

Table 4

Anatomic site	<50 years of age Person-years=9,339			≥50 years of age Person-years=4,830			P-heterogeneity
	N	Expected	SIR (95% CI)	N	Expected	SIR (95% CI)	
All sites, except nonmelanoma skin	24	10.93	2.2 (1.4–3.2)	80	41.25	1.9 (1.6–2.4)	0.58
Oesophagus	2	0.06	31.3 (5.2–103.3)	0	0.52	0	0.01
Colon	1	0.40	2.5 (0.1–12.5)	9	3.08	2.9 (1.4–5.4)	0.98
Pancreas	1	0.14	7.4 (0.4–36.3)	3	1.13	2.6 (0.7–7.2)	0.42
Lung	3	0.60	5.0 (1.3–13.5)	7	5.38	1.3 (0.6–2.6)	0.08
Central Nervous System	2	0.61	3.3 (0.5–10.8)	5	0.98	5.1 (1.9–11.3)	0.64
Brain	2	0.49	4.1 (0.7–13.5)	5	0.84	6.0 (2.2–13.2)	0.69
Eye	0	0.05	0	2	0.12	17.1 (2.9–56.5)	0.49
Thyroid gland	1	0.22	4.5 (0.2–22.1)	2	0.20	10.0 (1.7–33.1)	0.56
Endometrium	5	0.14	35.6 (13.0–78.9)	6	1.31	4.6 (1.9–9.5)	0.003
Ovary, tube and broad ligament	0	0.34	0	7	1.02	6.9 (3.0–13.6)	0.14

^a anatomic sites presented in this table are those with a statistical significant excess risk overall, or sites with an age-specific risk