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A Population-based survey of risk for cancer in individuals diagnosed with myotonic dystrophy

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Abstract

Introduction—The risk of cancer in patients diagnosed with myotonic dystrophy (DM) is reported for the homogeneous Utah population.

Methods—Clinical data accessed from the largest Utah healthcare providers have been record-linked to the Utah Population Database (UPDB), a population-based resource also linked to the Utah Cancer Registry. Relative risks were estimated for 36 cancers of different types in 281 DM patients.

Results—Testicular cancer (RR=10.74; 95% CI: 1.91, 38.79), endometrial cancer (6.98; 1.24, 25.22), and Non-Hodgkins lymphoma (4.25; 1.16, 12.43) were all observed at significant excess in DM patients.

Discussion—This study confirms an overall increased risk of cancer in DM. Individuals diagnosed with DM might benefit from risk counseling.

Search terms

myotonic dystrophy; relative risk; neuromuscular disease; UPDB; cancer

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Introduction

The Myotonic dystrophies (DM) are autosomal dominant, multi-systemic disorders characterized by progressive skeletal muscle weakness, delayed muscle relaxation (myotonia), and early onset cataracts¹. Recent studies and case reports have shown evidence of an increased risk of cancer in individuals with myotonic dystrophy (DM)^{2–13}. Initial investigations of increased cancer risk in DM focused on specific tumors. For example, in 1965 Cantwell and Reed described an association between pilomatricomas, benign skin tumors of the hair follicles, and DM¹². While pilomatricomas are rare and account for less than 1% of all benign skin tumors, numerous case reports (over 35 published, with multiple tumors present in 31 of these cases) establish pilomatricoma as a commonly developed neoplasm among individuals with DM⁷.

Four research groups have formalized their investigations of risk for cancer in DM patients. In a study of 1658 patients with DM in Swedish and Danish registries, Gadalla et al. describe a significantly increased risk of endometrial, brain, colon, and ovarian cancers in individuals with DM along with possible excesses of eye, thyroid, pancreatic, and other female genital organ cancers⁸. In a clinic-based study of 307 cases of DM at the Mayo Clinic, Win et al. found an increased risk of thyroid cancer and choroidal melanoma in individuals with DM and possible excesses of testicular and prostate cancers⁹. Mohamed et al. conducted a retrospective study of 109 French DM patients and found an increased risk of endometrial and lung cancers¹¹. Zampetti et al. investigated risk of skin cancer using 90 DM cases and 103 age- and sex-matched controls and found significantly higher numbers of nevi, dysplastic nevi, melanoma, and pilomatixoma among the cases¹³. The conclusions of these studies support the hypothesis of an increased risk of cancer in individuals with DM.

A population-based resource with linked diagnosis data, the Utah Population Database (UPDB), was analyzed to investigate the hypothesis of increased risk for cancer in DM patients. This study is distinguished from previous studies in that it considers existing data for a homogeneous population in the United States.

Materials and Methods

The UPDB is a computerized resource consisting of various data for over 7 million individuals. Individual records are derived from multiple data sources, including the Utah Cancer Registry (UCR), Utah vital records (birth and death certificates), Utah driver license data, and electronic medical records from the largest Utah hospitals and clinics¹⁴. Genealogy data for the original Utah pioneers and their descendants comprise 1.6 million records. With ongoing creation of genealogy from collection of vital statistics data (e.g. father, mother, and child from birth certificate), the genealogy resource has grown. Currently 4.2 million individuals in the UPDB are linked to pedigrees with at least 3 generations of data; these individuals were used for all analyses presented.

The UCR stores data on all independent primary cancer diagnoses within the state of Utah; approximately 60% of cancer patients link to genealogical data. In 1973, the UCR became a National Cancer Institute Surveillance Epidemiology and End Results (SEER) site¹⁶. Cancer

data in the UCR includes primary site, histology, age at diagnosis, stage, grade, survival, and treatment data.

Clinical data utilized for this study also came from the two largest health care providers in Utah, the University of Utah Health Sciences Center (UUHSC) and Intermountain Healthcare (IH), for which data from 1994 is record-linked to the UPDB. Using presence of an ICD-9 diagnosis code of 359.21 for DM (both type-1 and type-2), all patients were ascertained. The 36 cancer sites considered were determined by site, morphology and behavior coding from the UCR as shown in Supplementary Table S1.

The method used to estimate RR of cancer by site in DM patients is a well-established approach for analyzing data within the UPDB^{16,17}. The RR of cancer in DM patients is defined as the ratio of the observed number of cancers in DM patients to the expected number of cancers, which is based on the population rate of each cancer estimated within the UPDB.

All individuals in the UPDB who connect to genealogy data were assigned to 1 of 136 cohorts based on sex, birth-state (Utah or not), and year of birth (5-year cohorts)—these variables have been determined to be related to both record-linking quality and rate of cancer. The cohort-specific rate for each cancer site was estimated as the number of individuals with the cancer type of interest in each cohort divided by the total number of individuals in the cohort. The expected number of cancers by site for the DM patients was obtained for each site by multiplying the number of DM patients in each cohort by the cohort-specific cancer rate, and then summing across all cohorts. Observed numbers of cancers by site for the DM patients were obtained by counting (without duplication) the number of DM patients with the cancer of interest. The ratio of observed to expected number of cancers is an unbiased estimator of the RR. With a null hypothesis of $RR = 1$, one-sided probabilities that $RR > 1$ were calculated, assuming that the number of observed cancer cases followed a Poisson random variable with a mean equal to the expected number of cases.

Research was limited to analysis of unidentifiable data. There was no contact with human subjects, and no informed consent was required. The University of Utah Institutional Review Board and the Resource for Genetic Epidemiologic Research approved the research.

Results

Two hundred seven individuals with DM who were identified using the UUHSC data, and 167 individuals with DM were identified in the IH data; 93 DM patients were present in both datasets. The combined dataset of UUHSC and IH data is comprised of 281 individuals with DM. There was no significant difference in sex or age at diagnosis between the UUHSC and IH patients (data not shown; $p=0.995$, Fisher's Exact Test; $p=0.558$, Student's t-test, respectively).

Seventeen cancers were observed in thirteen DM patients in the combined UUHSC/IH dataset of 281 DM patients. Observed cancers among DM patients included cervical, colon, rectum, melanoma, endometrial, prostate, testis, thyroid, chronic lymphocytic leukemia,

acute lymphocytic leukemia, and Non-Hodgkins lymphoma. Relative risk estimates for these cancers in the DM patients are summarized in Table 1 and indicate that DM patients are at a significantly increased risk of developing testicular cancer ($p=0.01533$, $RR = 10.74$; $CI: 1.91, 38.79$), endometrial cancer ($p=0.03397$, $RR = 6.98$; $CI: 1.24, 25.22$), and non-Hodgkins lymphoma ($p=0.03478$, $RR = 4.25$; $CI: 1.16, 12.43$). There was suggestive evidence of increased risk of developing chronic lymphocytic leukemia ($p=0.07570$, $RR=12.70$; $CI: 0.65, 70.78$). Observed and expected numbers of cancers < 5 are not reported to protect patient confidentiality; no cancer sites were observed in more than 5 of the 281 DM cases.

Discussion

This population-based analysis of cancer risk among individuals diagnosed with DM provides evidence that individuals with DM are at significantly increased risk for testicular cancer, endometrial cancer, and non-Hodgkins lymphoma; there is also suggestive evidence that individuals with DM are at increased risk for chronic lymphocytic leukemia (Table 1).

These results replicated the increased risk of endometrial cancer reported in both the Swedish and Danish patient registries and in French patients^{10,11} and confirm the increased risk for testicular cancer for which evidence was only in the Mayo study⁹. The increased risk of pilomatricomas noted in various case reports and studies could not be assessed in this study because benign tumors are not included in the UCR.

In the appropriate clinical context, also taking into account the estimated increased risk for cancer in aging individuals and in those with a positive family history, individuals with DM may need to be counseled about this increased risk and prompted to adhere to current cancer screening guidelines. Unfortunately, there are insufficient screening assays for endometrial cancer and non-hodgkin's lymphoma. However, in men with DM, recommendation of testicular self-exam is an inexpensive method to combat this increased risk.

The mechanism behind the increased risk for some cancers is unclear. The testis are affected in DM, and men may have hypogonadism. The relationship between hypogonadism and the risk of testicular cancer is unclear. One possibility is that the sequestration of the muscleblind family of splicing factors (*MBNL1*, *MBNL2*, and *MBNL3*) by the toxic RNA repeat and upregulation of *CELF1* may lead to upregulation of B-catenin via the *Wnt* signaling pathway⁷. Another possibility is that the same cellular mechanism that allows for germline and somatic expansion of the CTG_n or CCTG_n repeat expansion in these individuals may lead to other unchecked DNA repair errors. Overall, the increased risk of cancer was found in disparate locations (blood, testes, and endometrium), suggesting that the risk is likely initiated at an intrinsic cellular pathway. Further investigation will be required to fully elucidate the mechanism.

Limitations of this study include the dependence on the presence of a diagnostic code in medical records to identify DM cases. Use of diagnostic coding to identify cases can result in both over, and under, ascertainment of cases. Furthermore, this diagnostic code does not allow separation of DM1 and DM2 cases. Data censoring is also possible, in that some

individuals could have been diagnosed with DM outside the UUHSC and IH diagnostic window (defined by the availability of data since 1994) or outside the state of Utah; cancers diagnosed outside Utah or before 1966 are also censored.

This manuscript provides confirmatory evidence of an increased risk of cancer in individuals with DM, replicates previous findings of an increased risk of endometrial cancer, validates earlier reports suggesting increased risk for testicular cancer and potentially identifies non-Hodgkins lymphoma as a new cancer sites of interest. Additional studies will be required to assess whether the increased risk of cancer is in both DM type-1 and type-2. Confirmation of these results should be sought in other populations. Given the substantial evidence, it is recommended that clinicians inform DM patients of, and monitor patients for, potential increased risk of cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DM	myotonic dystrophy
DM1	myotonic dystrophy type 1
DM2	myotonic dystrophy type 2
IH	Intermountain Healthcare
RR	relative risk
SEER	Surveillance Epidemiology and End Results
UCR	Utah Cancer Registry
UPDB	Utah Population Database
UUHSC	University of Utah Health Sciences Center

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Table 1

One-sided p-values, estimated relative risks, and 95% confidence intervals for cancer sites observed in at least one of the 281 DM patients.

Cancer	p-value	RR	95% CI
Any Cancer	0.05156	1.59	(1.00, 2.58)
Colon	0.37174	2.15	(0.11–11.99)
Rectum	0.19694	4.56	(0.23–25.40)
Melanoma	0.68810	0.89	(0.00–4.20)
Cervical	0.48627	1.50	(0.08–8.37)
Endometrial	0.03397	6.98	(1.24–25.22)
Prostate	0.40778	1.43	(0.25–5.16)
Testis	0.01533	10.74	(1.91–38.79)
Thyroid	0.09923	3.78	(0.67–13.65)
Chronic lymphocytic leukemia	0.07570	12.70	(0.65–70.78)
Acute lymphocytic leukemia	0.10796	8.75	(0.45–48.77)
Non-Hodgkins lymphoma	0.03478	4.25	(1.16–12.43)