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Cancer Phenotype in Myotonic Dystrophy Patients: Results from a Meta-analysis

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Abstract

Introduction—Recent studies provided evidence that patients with myotonic dystrophy (DM) are at excess risk of cancer. However, inconsistencies regarding affected anatomic sites persist.

Methods—We performed a meta-analysis of cancer risk in DM, searching studies published between January 1, 1990 and December 31, 2016. Eligible studies were full reports of DM cohorts with site-specific risks..

Results—The analysis included 5 studies, comprising 2,779 patients. Risk estimates for cancers of the endometrium and cutaneous melanoma were reported in all studies. The pooled standardized incidence ratio (pSIRs) for endometrial cancer =7.48, 95% confidence interval (CI) =4.72–11.8; and for cutaneous melanoma=2.45, 95%CI=1.31–4.58. Among cancers reported in 4/5 studies, elevated cancer risks were observed for thyroid (pSIR=8.52, 95%CI=3.62–20.1), ovarian (pSIR=5.56, 95%CI=2.99–10.3), testicular (pSIR=5.95, 95%CI=2.34–15.1), and colorectal (pSIR=2.2, 95%CI=1.39–3.49).

Discussion—Our data refined the DM cancer phenotype, which may guide patient clinical management and inform plans for molecular investigations to understand DM-related carcinogenesis.

Keywords

Myotonic dystrophy; cancer; neoplasms; nucleotide repeat disorders; meta-analysis

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines

INTRODUCTION

Myotonic dystrophy (*dystrophia myotonica*; DM) is an autosomal dominant multisystem disorder which presents clinically with muscle weakness and myotonia¹. The disease is caused by a tri-nucleotide repeat expansion in the dystrophia myotonica-protein kinase (*DMPK*) gene in DM type 1 (DM1)²⁻⁴, or a tetra-nucleotide repeat expansion in the zinc finger 9 (*ZNF9*) gene in DM type 2 (DM2)⁵. The size of the nucleotide repeat expansion in DM1, but not DM2, is modestly correlated with disease severity and age at onset; congenital DM is the most severe form of the disease⁶. The phenotypic complexity of this disease may result from splicing dysregulation in the pre-mRNA of multiple genes⁷⁻⁹.

Case reports and small case series suggested that cancer might be part of the DM clinical phenotype¹⁰. Recently, several epidemiological studies provided quantitative support for this notion¹⁰⁻¹⁴. However, there are inter-study inconsistencies regarding the specific sites of increased cancer involvement. It is possible that smaller studies were under-powered to detect rare cancers - such as those of the brain or ovary - detected in larger DM studies. A recent study of 1,119 DM patients from Sweden showed that DM patients are at 5-fold excess risk of brain cancer when compared with the general population¹⁵.

A precise listing of DM-related cancers is important for patient clinical management, since they represent the third leading cause of death in those patients^{16,17,15}. Additionally, this knowledge may guide the planning for molecular studies aiming at understanding DM-related carcinogenesis. Here, we used meta-analysis tools to pool cancer site-specific risk estimates across 5 relevant published studies.

MATERIALS AND METHODS

Data Sources and Study Selection

We searched three different databases (Medline, Cochrane Library, Embase) for the terms “myotonic dystrophy”, “Steinert’s disease”, “cancer”, “malignancy”, “neoplasm”, “tumor”, “carcinoma”, “sarcoma”, “lymphoma”, “risk” from the period January 1, 1990 through December 31, 2016. Reference lists from the reports retrieved were examined and additional references included if pertinent. No language restriction was applied. This initial search was completed by an experienced librarian, and abstracts were screened by JIE. Selected full text were reviewed by JIE and SMG. The inclusion criteria of selected studies for this analysis were: 1) full reports, 2) DM cohorts (independent on disease subtype), 3) reported site-specific cancers.

Data Extraction and Synthesis

We used a standardized abstraction form to extract the following: first author, year of publication, country, number of DM patients, age at DM and at cancer diagnosis, basis for DM diagnosis, source of cancer ascertainment, relative risks (RRs) or standardized incidence ratios (SIRs) with corresponding 95% confidence intervals (CIs) for cancer risk for all organs combined, when available, and for all available cancer-site specific estimates. We used a two-stage approach for data extraction to ensure accuracy; the first extraction was

carried out by JIE and then information was checked by SMG. Disagreements were resolved by consensus discussion.

Statistical Analysis

Study-specific SIRs with 95% CIs for all cancers combined and for specific cancer sites were aggregated using random effect models when significant heterogeneity was detected; otherwise fixed effect models were used. Organ-specific SIRs were combined only if at least three studies reported estimates for that type of cancer. Unreported 95% CIs were calculated using the Poisson distribution based on observed and expected numbers of cancer. We assessed the heterogeneity between cohorts by the Cochran Q test and I^2 statistic. Heterogeneity was considered significant when $P < 0.05$ for Cochran Q test or $I^2 > 50\%$. In rare situations in which heterogeneity was caused by a particular study, we reported pooled SIR (pSIR) with and without the study of concern. We stratified our analyses by continent (USA *versus* Europe) and by type of study (clinic-based *versus* population-based) to test the effect of these factors on result heterogeneity.

All analyses were performed using STATA-SE 14 (Stata Corp LP, College Station, TX)

RESULTS

A total of 35 studies were screened for inclusion; 22 were judged irrelevant, leaving 13 studies for eligibility assessment. We excluded studies with self-reported cancers or prevalence estimates (these studies mainly focused on identifying risk factors for tumor development), those with no comparison group for cancer risk calculations (cancer absolute risk studies), and a study assessing risk in DM relatives. Figure 1 describes study selection scheme.

Our final pool included 5 cohort studies (2 clinic-based, and 3 population-based). The largest comprised 1,658 DM patients identified primarily from inpatient hospital records in Sweden and Denmark, and provided the initial evidence supporting an excess cancer risk of the following cancers: endometrial (SIR=7.6, 95%CI=4.0–13.2), ovarian (SIR=5.2, 95%CI=2.3–10.2), brain (SIR=5.3, 95%CI=2.3–10.4), and colon (SIR=2.9, 95%CI=1.5–5.1). Possible excesses of thyroid (SIR=7.1, $p=0.01$), ocular melanoma (SIR=12.0, $p=0.01$), and pancreatic cancer (SIR=3.2, $p=0.05$) were also reported, none of which reached statistical significance after adjusting for multiple comparisons.¹¹ Win *et al.*, (307 DM patients) replicated the elevated risks of thyroid and eye cancer, and suggested a possible testicular cancer risk (SIR=5.1, $p=0.06$)¹². Two subsequent smaller studies from France ($n=109$) and the US ($n=281$) replicated the endometrial cancer finding (both studies), and that of testicular cancer (only the US study)^{13,14}. The study by Abbott *et al.*, also suggested that DM patients may be at excess risk of non-Hodgkin lymphoma (NHL; SIR=4.25, 95%CI=1.16–12.43)¹⁴, while Mohamed *et al.* suggested an association with lung cancer (RR=6, 95%CI=1.2–17.7)¹³. Most recently, a study from northern Spain (424 patients with genetically confirmed DM1) replicated the results of the original study, except that the positive colorectal cancer association (SIR=2.06, 95%CI=0.94–3.92), did not quite achieve statistical significance, and the thyroid cancer association (SIR 23.33, 95%CI 9.38–48.08)

was stronger¹⁵. Table 1 summarizes the design and patient characteristics for each of the selected studies

Pooled cancer risk estimates

Risk estimates for only 2 cancer sites (endometrium; cutaneous melanoma) were reported by all 5 studies. Pooled risk estimates showed that DM patients were at significantly increased risk of both cancers ($p < 0.001$ for endometrium; and $p = 0.005$ for cutaneous melanoma) (Figure 2A, B).

For cancers reported by 4 studies, the highest risk estimate was for thyroid cancer ($p < 0.001$); however, significant inter-study heterogeneity was observed ($I^2 = 60\%$, $p = 0.06$). Results from a random effects model attenuated the effect sizes, but risks remained high and statistically significant ($pSIR = 8.52$, $p < 0.001$). Other cancers occurring excessively included ovary, testis ($p < 0.001$), and colon/rectum ($p = 0.001$) (Figure 3A–D).

Supplemental eTable 1 summarizes pooled SIRs by cancer anatomic site for cancers that were reported in at least 3 studies, along with measures of heterogeneity. For these, our analysis suggested elevated risks for brain cancer and non-Hodgkin lymphoma. Pooled results for breast, prostate, lung, kidney, and leukemia should be interpreted with caution, since wide confidence intervals were observed, indicating imprecise point estimates.

Sensitivity analyses and publication bias

We performed several stratified meta-analyses for results with significant heterogeneity (risk estimates for cancers of the thyroid, lung, and prostate). We stratified by geographic region (USA *versus* Europe) and by type of study (clinic-based *versus* population-based).

For thyroid cancer, the heterogeneity was due entirely to European studies (Supplemental eFigure 1A). In fact, excluding the study from Fernandez-Torron *et al.* diminished the I^2 to zero. Results after exclusion still supported an excess risk of thyroid cancer in DM patients ($pSIR = 5.56$, 95%CI=2.82–10.95). For prostate cancer, studies from USA showed higher SIRs than studies from Europe, and heterogeneity disappeared with stratified analysis by continent subgroup (Supplemental eFigure 1B); however, the results from stratified analyses remained inconsistent. In the case of lung cancer, the heterogeneity remained in the clinic-based subgroup, with no heterogeneity in the population-based subgroup (Supplemental eFigure 1C), but results were inconclusive.

Funnel plots for endometrial cancer and cutaneous melanoma are included (Supplemental eFigure 2). Yet, reliable assessment of publication bias was not possible because of the small number of studies included in this meta-analysis.

DISCUSSION

This meta-analysis sought to clarify which specific cancers might comprise components of the DM phenotype, to inform both patient management and translational research aimed at understanding DM-associated carcinogenesis. This association is relatively new, and the relatively small sample sizes for 4 of the 5 published studies to date made it difficult to infer

the answer to the phenotype question. Pooled estimates using 2,779 patients from 5 DM cohorts (3 European from 4 countries, 2 US) demonstrated significant, consistent excesses of cancers of the thyroid, endometrium, ovary, cutaneous melanoma, colon/rectum, and testis (at least 4 cohorts included in the analysis), plus possibly brain cancer, and non-Hodgkin lymphoma (3 cohorts included).

The largest to-date epidemiological investigation of cancer risk in DM showed a statistically significant excess risk for cancers of the endometrium, ovary, brain, and colon.¹¹ Those four cancers present a pattern reminiscent of that seen in Lynch syndrome¹⁸, raising the possibility that an abnormality of DNA mismatch repair might underlie their occurrence. Several subsequent smaller studies validated some, but not all, of the original findings, and suggested the possibility of other affected organs.^{12,13,14,15} Inconsistencies between studies regarding specific cancer associations may be due to selection bias in clinic-based studies, diagnosis misclassification in registry studies, or differences in patient characteristics; *e.g.*, DM severity, or DM subtype. A cross-sectional analysis of a large DM study including 781 DM1 and 130 DM2 patients showed that tumor risk is higher in DM1 than DM2, and suggested different tumor profiles in the two subtypes²¹. Studies included in this meta-analysis were expected to be skewed toward DM1 patients since DM1 is more common (2 studies included DM1 only, 2 studies included all DM patients, unknown subtype, and 1 study included a subset of known DM2 patients). The study by Win *et al.*, showed that DM2 patients (n=86) are at excess risk of prostate cancer (SIR=3.36, p=0.008) and possibly thyroid (SIR=5.7, p=0.05)¹². Cancer risk in patients with DM2 is still undefined and needs to be studied in a large well-designed study.

It is also possible that some of the findings were confounded by unmeasured behavioral risk factors, *e.g.*, smoking and lung cancer, exogenous hormones and endometrial or ovarian cancer, *etc.* Several studies looking at the effect of known risk factors on DM cancer risk, all sites combined, found no association with smoking, alcohol, or body mass index^{21–23}. However, a recent analysis of skin cancer risk factors in DM patients observed increased risks in subjects reporting a blistering sunburn following sun exposure (OR=4.28, 95%CI=0.91–19.95, P=0.06)²⁴. Large, well-designed studies of genetically-confirmed DM patients with comprehensive risk factor information are needed to investigate the possible interactions between genetically-predisposed DM patients and environmental exposures in DM-related carcinogenesis.

The molecular mechanism underlying DM-carcinogenesis is still unclear. Perhaps the most appealing hypothesis is that DM alternative splicing abnormality may alter the expression of oncogene or tumor suppressor genes. As a possible example, Fernández-Torrón and colleagues described differential transcription/expression of several cancer-associated genes (*PDK4*, *DAPK1*, *CASP5* and *PLA2G7*) in DM1 patients, and observed that the 200c/141microRNA tumor suppressor family was down regulated in female DM1 patients¹⁵. It was also suggested that cancer in DM is part of a generalized premature aging phenotype²⁵, a hypothesis that yet to be tested. Translational research efforts aimed at elucidating the molecular biologic basis for recently-recognized DM-related carcinogenesis comprise a fertile domain for identifying novel cancer pathogenesis pathways.

There are limitations to this study. Meta-analysis is a powerful statistical approach to synthesizing evidence from pooling results across studies and identifying sources of inter-study heterogeneity; nonetheless it is limited by its inability to answer new questions or to overcome deficiencies in published literature. Additionally, it is prone to the effect of publication bias.²⁶ The small number of included studies limited our ability to effectively study such bias. Our study is also limited by the absence of site-specific cancer risk estimates for all anatomic sites in all published studies, which may result in over-estimating the risks, since unpublished associations tend to be null. Here, we focused explicitly on cancers reported in at least 3 of the 5 existing studies, to minimize this concern.

In conclusion, this meta-analysis confirms that DM patients are at high risk of specific malignancies, including cancers of the thyroid, endometrium, ovary, cutaneous melanoma, colon/rectum, testis, and possibly, brain cancer and non-Hodgkin lymphoma. A larger, well-designed study of genetically-confirmed DM patients is needed to confirm these findings. This analysis reasonably designates the above cancers as those most clearly associated with DM, comprising the best target for etiologically-oriented laboratory research efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

DM	myotonic dystrophy
pSIRs	pooled standardized incidence ratio
CI	confidence interval
DMPK	dystrophin myotonic-protein kinase
DM1	myotonic dystrophy type 1
ZNF9	zinc finger 9
DM2	Myotonic dystrophy type 2
RR	relative risk
SIR	standardized incidence ratio

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Figure 1.
Flow chart of study selection

Figure 2.

Forest plots for the risk of cancers reported in all 5 published studies; a) endometrial cancer; b) cutaneous melanoma. Shaded boxes represent study-specific standardized incidence ratios and lines represents the 95% confidence interval (CI). The pooled SIR is represented by a diamond with its width corresponding to 95% CI bounds. Note: Number of cancers in the study by Abbott et al.,¹⁴ were not available due to the regulations of the Surveillance, Epidemiology, and End Results (SEER) Program for reporting small numbers.

Figure 3.

Forest plots for the risk of cancers reported in 4/5 published studies; a) thyroid cancer; b) testicular cancer; c) ovarian cancer; d) colorectal cancer. Shaded boxes represent study-specific standardized incidence ratios and lines represents the 95% confidence interval (CI). The pooled SIR is represented by a diamond with its width corresponding to 95% CI bounds. Note: Number of cancers in the study by Abbott et al.,¹⁴ were not available due to the regulations of the Surveillance, Epidemiology, and End Results (SEER) Program for reporting small numbers.

Table 1

Summary of selected information from studies included in the meta-analysis

Reference Number	Country	Number of DM (N subtype)	Men/Women	Study Calendar Years	DM Identification	Cancer Ascertainment	Age at DM/start of follow-up	Age at Cancer Diagnosis
11	Sweden, Denmark	1658 (NA)	861/797	1977–2008	Hospital Patient Registry	National Cancer Registry	Median=46 years (Sweden) and 38 (Denmark)	Median=57 years
12	US	307 (118 DM1, 86 DM2, 103 type unknown)	142/165	1993–2010	Mayo Clinic medical records	Mayo Clinic medical records	Mean= 39.6 years	Median=55 years
13	France	109 (all DM1)	50/59	1998–2011	Hôpitaux de Brabois medical records	Hôpitaux de Brabois medical records	Mean= 44 years	NA
14	US	281 (NA)	NA	1994–NA	Utah Population Database	Utah Cancer Registry	NA	NA
15	Spain	424 (all DM1)	210/214	1985–2013	Gipuzkoa cohort of DM1	Patient medical Records	NA	Mean=46.6 years

NA: not available; DM1: myotonic dystrophy type1; DM2: myotonic dystrophy type2