

## Brief Report

# Cancer risk among patients with hereditary muscular dystrophies: a population-based study in Taiwan, 1997–2009

Gen-Min Lin<sup>1,2</sup> and Yi-Hwei Li<sup>1</sup>

## Abstract

Muscular dystrophies (MD) comprise a heterogeneous group of hereditary myopathic diseases. In this group, myotonic MD is associated with an increased cancer risk. However, the cancer risk in other types of MD is unclear. To address this gap in knowledge, we assessed data obtained from the Taiwan Health Insurance Program database. A total of 1,272 patients with MD diagnosed between 1997 and 2009 were enrolled. They were followed up for cancer during the same period by record linkage with the cancer certification in Taiwan. Age- and sex-standardized incidence ratios (SIRs) of overall and site-specific cancers were calculated. For congenital and progressive hereditary MD, there were 685 and 505 cases (males: 69.5% and 80.6%), the median ages at diagnosis were 16 and 13 years, and the mean follow-up durations were 7.12 and 5.06 years, respectively. In addition, cancers were developed in 10 patients with congenital MD and 3 patients with progressive hereditary MD. Female MD patients exhibited an increased cancer risk, yielding an SIR of 3.37 [95% confidence interval (CI) = 1.38–8.25] in congenital MD and 2.95 (95% CI = 0.95–9.19) in hereditary progressive MD. Site-specific cancer SIRs were not powered to be significantly different. In conclusion, genetic defects in hereditary MD may increase cancer risks in females and a sex difference should be further investigated.

**Key words** Cancer risk, muscular dystrophies, standardized incidence ratio

Muscular dystrophies (MD) comprise a heterogeneous group of hereditary myopathic diseases characterized by progressive skeletal muscle weakness, muscle protein defects, and muscle cell death<sup>[1]</sup>. Congenital MD (ICD-9-CM code: 359.0), in which hypotonia occurs at birth or during infancy, is mainly inherited in an autosomal recessive manner, with the exception of collagen VI-deficient and Lamin A/C gene (LMNA)-related types<sup>[2]</sup>. Progressive hereditary MD (ICD-9-CM code: 359.1) is composed of one type of X-linked recessive disorder that occurs in early childhood and another type known as limb-girdle MD that develops in early adulthood. Myotonic MD (ICD-9-CM code: 359.2) is an autosome-dominant disorder, and symptoms usually develop in the second decade of life<sup>[3]</sup>.

Recently, myotonic MD has been observed with an increased cancer risk in Swedish and Danish cohorts; however, the cancer

risks for other MD types were unclear<sup>[4-6]</sup>. Therefore, we performed a population-based study in Taiwan to quantify the cancer risk in patients with MD. We hypothesized that genetic defects in MD may promote cancer development.

## Materials and Methods

We used a longitudinal health insurance database for people with “catastrophic illnesses” including MD and cancer provided by the Taiwan Health Research Institute. Patients newly diagnosed with MD and free of cancer would be eligible in our cohort (ICD-9-CM codes: 359.0–359.2). We skipped the first two years’ data of the Health Insurance Program in Taiwan to ensure new MD cases and selected individuals whose first-ever issue of MD certificate occurred during the period 1997–2009. The first-ever cancer status was also obtained by linkage to the catastrophic illness database (ICD-9-CM codes: 140–208). We calculated background cancer incidences for the general population from the cancer registry provided by the Bureau of Health Promotion in Taiwan during the same period. Age- and sex-standardized incidence ratios (SIRs), taken as the observed number of cases divided by the expected number of cancer cases, were used as measures of relative risk, and 95% confidence interval (CI)

**Authors’ Affiliations:** <sup>1</sup>Department of Public Health, Tzu-Chi University, Hualien, Taiwan; <sup>2</sup>Department of Medicine, Hualien Armed Forces General Hospital, Hualien, Taiwan.

**Corresponding Author:** Yi-Hwei Li, Department of Public Health, Tzu-Chi University, Zhongyang Road 701, Section 3, Hualien 97004, Taiwan. Tel: +886-3-8565301-2271; Fax: +886-3-8564041; Email: yihwei@mail.tcu.edu.tw.

**doi:** 10.5732/cjc.013.10156

was calculated after assuming a Poisson distribution of the observed number of cancers. The SAS statistical software (SAS System for Windows, version 9.1.3; SAS Institute, Cary, NC, USA) was used to perform statistical analysis. A *P* value of < 0.05 was considered significant.

## Results

**Table 1** demonstrates the characteristics of patients with MD (ICD-9-CM codes: 359.0–359.2). Because myotonic MD (ICD-9-CM code: 359.2) was not considered a catastrophic illness until 2005, only 82 patients were registered and no cancer was observed in this group. For congenital MD (ICD-9-CM code: 359.0) and progressive hereditary MD (ICD-9-CM code: 359.1), there were 685 and 505 cases (males: 69.5% and 80.6%), the median ages at diagnosis were 16 and 13 years, and the mean follow-up durations were 7.12 and 5.06 years, respectively. **Table 2** shows the cancer risk in patients with MD by sex. Cancers were reported in 10 patients with congenital MD and in 3 patients with progressive hereditary MD during the study period. Females exhibited an increased cancer risk, yielding an SIR of 3.37 (95% CI = 1.38–8.25, *P* = 0.008) in congenital MD and 2.95 (95% CI = 0.95–9.19, *P* = 0.062) in hereditary progressive MD. Site-specific cancer SIRs were not powered to be significantly different.

Eleven of the 13 cancers occurred after 40 years of age.

## Discussion

We report here a population-based study with the largest sample of congenital and hereditary progressive MD cases to date to address their cancer incidence ratios relative to general population in Taiwan. As an innate limitation, age at diagnosis is merely a proxy variable for the actual age of onset in MD patients. The median age at diagnosis of MD patients was practically higher than the expected age of onset. Furthermore, we could not identify the exact MD subtype based on the ICD-9-CM code numbers. Accordingly, it is difficult to explain why the median age at diagnosis of patients with congenital MD was paradoxically older than that of patients with hereditary progressive MD. Regardless of these pitfalls, the study is still reliable to test the hypothesis that genetic defects in MD may be associated with an increased cancer risk. First, the statistical power for cancer risk may be underestimated because of a time lag for MD diagnosis. Second, if the dataset of MD (ICD-9-CM codes: 359.0–359.1) are combined to eliminate misclassifications, there will be no bias for total cancer risk in each sex population, yielding an SIR of 3.18 (95% CI = 1.57–6.46, *P* = 0.001) for females and 1.07 (95% CI = 0.44–2.63, *P* = 0.876) for males.

**Table 1. Characteristics of patients with muscular dystrophy**

Item	Congenital MD (ICD-9-CM code: 359.0)	Progressive hereditary MD (ICD-9-CM code: 359.1)	Myotonic MD (ICD-9-CM code: 359.2)
Total (cases)	685	505	82
Males [cases (%)]	476 (69.5)	407 (80.6)	50 (61.0)
Total follow-up (person-years)	4,874.3	2,557.6	280.6
Mean follow-up (years)	7.12	5.06	3.42
Median age at diagnosis of MD (years, Q1–Q3)	16 (7–31)	13 (7–32)	38.5 (26–45)

MD, muscular dystrophy; ICD, the International Classification of Diseases.

**Table 2. Cancer risk of patients with muscular dystrophy by sex**

Item	Congenital MD (ICD-9-CM code: 359.0)		Progressive hereditary MD (ICD-9-CM code: 359.1)		Myotonic MD (ICD-9-CM code: 359.2)	
	Male	Female	Male	Female	Male	Female
Median age at diagnosis of MD (years, Q1–Q3)	15 (8–28)	19 (7–34)	10 (7–25)	33 (19–47)	34 (24–40)	42 (34–48)
Total cases of cancers during follow-up	5	5	0	3	0	0
Incidence per 10,000 person-years	14.81	33.36	0	61.61	0	0
SIR (95% CI)	1.51 (0.61–3.69)	3.37 (1.38–8.25)	0	2.95 (0.95–9.19)	0	0
<i>P</i> value	0.363	0.008	0	0.062	0	0

SIR, standardized incidence ratio; CI, confidence interval. Other abbreviations as in Table 1.

In our study, only female patients showed an increased cancer risk. This finding is in contrast to that of Gadalla *et al.*<sup>[6]</sup>, which showed that both male and female patients with myotonic MD have an increased cancer risk. This disparity may be reasoned by small samples of male patients and a high mortality in affected males with X-linked recessive MD in early adulthood, leading to a reduced cancer incidence<sup>[7,8]</sup>. Interestingly, most cancers were observed after 40 years of age, supporting that a longer life span is needed for cancer development.

In conclusion, genetic defects in hereditary MD may increase cancer risks in females, and a sex difference should be further

investigated.

## Acknowledgments

This study was based in part on data from the Taiwan Health Insurance Research database. The interpretations and conclusions contained do not represent the Taiwan Health Insurance Research.

Received: 2013-08-28; revised: 2013-11-17;  
accepted: 2013-11-26.

## References

- [1] Emery AE. The muscular dystrophies. *Lancet*, 2002,359:687–695.
- [2] Sparks SE, Escolar DM. Congenital muscular dystrophies. *Handb Clin Neurol*, 2011,101:47–79.
- [3] Amato AA, Griggs RC. Overview of muscular dystrophies. *Handb Clin Neurol*, 2011,101:1–9.
- [4] Mueller CM, Hilbert JE, Martens W, et al. Hypothesis: neoplasms in myotonic dystrophy. *Cancer Causes Control*, 2009,20:2009–2020.
- [5] Zemtsov A. Association between basal, squamous cell carcinomas, dysplastic nevi and myotonic muscular dystrophy indicates an important role of RNA binding proteins in development of human skin cancer. *Arch Dermatol Res*, 2010,302:169–170.
- [6] Gadalla SM, Lund M, Pfeiffer RM, et al. Cancer risk among patients with myotonic muscular dystrophy. *JAMA*, 2011,306:2480–2486.
- [7] McMillan HJ, Campbell C, Mah JK, et al. Duchenne muscular dystrophy: Canadian paediatric neuromuscular physicians survey. *Can J Neurol Sci*, 2010,37:195–205.
- [8] Centers for Disease Control and Prevention (CDC). Prevalence of Duchenne/Becker muscular dystrophy among males aged 5-24 years—four states, 2007. *MMWR Morb Mortal Wkly Rep*, 2009, 58:1119–1122.