J Neurol (2016) 263:492–498
DOI 10.1007/s00415-015-8006-y

ORIGINAL COMMUNICATION

Increased risk of tumor in DM1 is not related to exposure to common lifestyle risk factors

Maria Laura Ester Bianchi[1] · Emanuele Leoncini[2] · Marcella Masciullo[3] · Anna Modoni[1] · Shahinaz M. Gadalla[4] · Roberto Massa[5] · Emanuele Rastelli[5] · Chiara Terracciano[5] · Giovanni Antonini[6] · Elisabetta Bucci[6] · Antonio Petrucci[7] · Sandro Costanzi[8] · Massimo Santoro[9] · Stefania Boccia[2] · Gabriella Silvestri[1]

Received: 17 June 2015 / Revised: 5 December 2015 / Accepted: 17 December 2015 / Published online: 6 January 2016

Abstract Recent studies documented an increased risk of neoplasm in patients with myotonic dystrophies (DM). Yet, none of these studies evaluated the contribution of common cancer risk factors in such observation. In this study, we included a cohort of patients ($n = 255$) with an established molecular diagnosis of DM type 1 (DM1), and who receives their treatment in one of the four centers with recognized expertise in neuromuscular disorders in Rome. We estimated the prevalence of benign and malignant tumors, and assessed if lifestyle factors and/or specific disease features would be associated to their occurrence. Overall, 59 benign tumors in 54 patients and 19 malignant tumors in 17 patients were diagnosed. The most common malignant neoplasms were cancers of the skin (31.6 %), thyroid (21.0 %), ovary (10.5 %), and breast (10.5 %). Uterine fibroid was the most common benign tumor (37.6 %) in women, while pilomatricoma was the most common in men (28.6 %). Age at enrollment (OR = 1.02, 95 % CI 1.00–1.05), and female gender (OR = 5.71, 95 % CI 2.90–11.22) were associated with tumor development in DM1 patients, while thyroid disorders was associated with malignant tumors only in women (OR = 5.12, 95 % CI 1.35–19.37). There was no association between tumor development and evaluated lifestyle factors. In conclusion, the lack of association between common cancer risk factors and tumor development in DM1 support a pathogenic link between tumors and DM1 itself, emphasizing the need for a systematic surveillance. Our observation of an association between thyroid diseases in women and cancer development needs confirmation.

Keywords Myotonic dystrophy type 1 · Tumor · Cancer · Thyroid disease · Risk factors

✉ Gabriella Silvestri
gsilvestri@rm.unicatt.it

1 Department of Geriatrics, Neuroscience and Orthopedics, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome, Italy

2 Institute of Public Health, Section of Hygiene, UCSC, Rome, Italy

3 IRCSS Fondazione Santa Lucia, Rome, Italy

4 Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

5 Department of Systems Medicine (Neurology), University of Rome Tor Vergata, Rome, Italy

6 Department of Neurosciences, Mental Health and Sensory Organs (NESMOS), Sapienza University of Rome, Rome, Italy

7 Unità Operativa Complessa Neurologia e Neurofisiopatologia, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy

8 Unit of Medical Genetics, Center for Neuromuscular and Neurological Rare Diseases, S. Camillo Forlanini Hospital, Rome, Italy

9 Fondazione Don Carlo Gnocchi Onlus, Milan, Italy

Introduction

Myotonic dystrophy type 1 (DM1), also known as Steinert's disease (OMIM #160900), and myotonic dystrophy type 2 (DM2) (OMIM #6026668) are dominantly inherited multisystem neuromuscular disorders, variably affecting the skeletal muscle, heart, eye, smooth muscle, endocrine, and central nervous system [1, 2]. Both disorders are caused by the pathological expansion of an unstable nucleotide repeat located in non-coding regions of their

respective genes (CTG repeats in the 3′ UTR of *DMPK*, on chr 19q in DM1, and CCTG repeat in intron 1 of *CNBP* in DM2) [1, 2].

In the past, several case reports emphasized the occurrence of certain tumors in patients with DM like pilomatricoma, a rare benign calcifying cutaneous neoplasm derived from hair matrix cells [3–6]. More recently, few epidemiological studies provided evidence of an increased risk of certain malignant neoplasms among DM patients [7–9]; specifically, cancers of thyroid, melanoma, endometrium, brain, ovary and colon cancer. A cross-sectional study using data collected from DM patients at enrollment to the U.S. Registry of Myotonic Dystrophy and Facioscapulohumeral Dystrophy Patients and Family Members, found that female patients or those having DM1 disease subtype were more likely to report having a history of tumor [10]. Additionally, this study reported that DNA repeat expansion size was not associated with tumor development in either DM1 or DM2 [10]. Another report from a hospital-based study including 109 DM1 patients showed similar results [9]. To our knowledge, the possible contribution of patients' lifestyle factors to the observed excess risk of cancers has not been assessed.

In this study, we assessed the prevalence of both benign and malignant tumors in a cohort of molecularly well-characterized Italian DM1 patients, and evaluated the role of common lifestyle factors and DM1 related clinical manifestations in tumor development.

Methods

Study population

All genetically confirmed DM1 patients who were >18 years and under active follow-up between January and December 2013 in one of the four main DM treating hospitals in Rome (Policlinico Gemelli, Policlinico Tor Vergata, Azienda Ospedaliera San Camillo, and Azienda Ospedaliera Sant'Andrea) were invited to participate in an in-person or telephone interview ($n = 274$). The method used for the molecular diagnosis of DM1 by *n*(CTG) repeat expansion for those patients are described elsewhere [11]. Eight patients did not consent to participate and eleven were excluded due to the lack of detailed medical information, resulting in a total of 255 DM1 patients included in this study. The study was conducted upon Hospital Review Boards approvals.

All interviews were conducted by a trained physician who filled a structured questionnaire including patient demographics, height and weight, smoking history, alcohol consumption, employment history, and patient history of benign or malignant tumors (questionnaire is included in supplementary data). A medical record and histology report review was conducted to confirm self-reporting tumor history. In addition, we extracted the following from patient record: age at DM onset, size of *n*(CTG) repeats in leukocytes, disease duration and selected extra-neurological manifestations of DM1 (type 2 diabetes and thyroid dysfunction). Patients with malignant tumors were asked to recall their lifestyle habit 12 months before cancer diagnosis or symptoms' presentation.

Statistical analysis

For univariate analyses, we used Kruskal–Wallis test for continuous variables, and Chi- square or Fisher's exact test for categorical variables comparing three categories of patients (those with no history of tumors, history of benign tumors only, and those with at least one malignant tumor). For multivariable analysis, we calculated odds ratios (ORs) and 95 % confidence intervals (CIs) of lifestyle and clinical factors adjusting for gender, age, and history of thyroid disease. We categorized the size of CTG trinucleotide repeat expansions into four subgroups: E1 if repeat size <150, E2 $\geq 150 < 1000$ repeats, E3 $\geq 1000 < 1500$ repeats, and E4 ≥ 1500 repeats, similar to our previous strategy [12, 13].

Statistical analyses were performed using Stata software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, StataCorp LP, TX). All statistical tests were two-sided, and p values <0.05 were considered statistically significant.

Results

The demographic and clinical data of the study participants are reported in Table 1. The study included 146 men (57.2 %) and 109 women (42.8 %); approximately 70 % of the patients were diagnosed at age younger than 29 years, and about 70 % had an E2 or E3 range of expansion size. The study included nine patients with congenital DM; all diagnosed before age 15 years. Myotonia (70 %) was the initial symptoms in most of the patients diagnosed between age 15–44 years followed by distal muscle weakness (15 %), bulbar symptoms (5–7 % of patients), and early onset cataract (8–10 %); while myotonia and cataract were the most common initial symptom in older patients.

Approximately one-fourth of the patients ($n = 63$, 24.7 %) reported a history of benign and/or malignant tumor (46 patients had benign tumors only, nine patients had malignant tumors only, and eight patients had both). In comparison with the age-matched general Italian population [14], we found a high prevalence of malignant tumors among DM1 patients (3.2 vs. 6.7 %, respectively).

The most commonly reported malignant neoplasms were cancers of the skin ($n = 6/19$; 31.6 %), thyroid ($n = 4/19$; 21.0 %), ovary ($n = 2/19$; 10.5 %), and breast ($n = 2/19$; 10.5 %). On the other hand, uterine fibroid was the most commonly reported benign tumor ($n = 41/59$) in women, while benign skin-specifically pilomatricoma-represented the most common benign tumor ($n = 2/9$) in the male patients (Table 2).

In univariate analysis comparing three categories of DM1 patients (those with benign tumors only, any malignant tumors vs. no tumors) (Table 3), women were more likely to have a history of benign ($n = 35/109, 32.1$ % vs. $n = 11/146$, 7.5 %, $p < 0.001$) or malignant tumors ($n = 12/109$, 11.0 % vs. $n = 5/146$, 3.4 %, $p = 0.016$). Older age ($p < 0.05$), or having a history of thyroid disease ($p < 0.01$)—including multinodular goiter or hypothyroidism—were statistically

Table 1 Demographic, clinical and molecular features of 255 myotonic dystrophy 1 (DM1) patients

	n	%
Female	109	42.8
Age (years)		
<30	32	12.6
30–39	47	18.4
40–49	89	34.9
50–59	51	20.0
>60	36	14.1
Missing	0	0.0
Age at initial DM1 symptoms (years)		
<15	61	26.9
15–29	96	42.3
30–44	57	25.1
>45	13	5.7
Missing	28	11.0
Body-mass index		
Underweight	5	2.1
Normal range	119	48.8
Overweight	73	29.9
Obese	47	19.3
Missing	11	4.3
Triplet expansion		
E1	44	19.1
E2	95	41.1
E3	61	26.4
E4	31	13.4
Missing	24	9.4
History of cancer		
No tumor	192	75.3
Malignant tumors	17	6.7
Patients with 1 malignant tumor	8	3.1
Patients with 2 malignant tumors	1	0.4
Patients with 1 malignant tumor and 1 benign tumor	7	2.7
Patients with 2 malignant tumors and 1 benign tumor	1	0.4
Benign tumors	54	21.2
Patients with 1 benign tumor	41	16.1
Patients with 2 benign tumors	5	2.0
Patients with 1 malignant tumor and 1 benign tumor	7	2.7
Patients with 1 benign tumor and 2 malignant tumors[a]	1	0.4
Missing	0	0.0

[a] 7 patients with 1 malignant tumor and 1 benign tumor, and 1 patient with 2 malignant tumors and 1 benign tumor, were included in both groups: malignant tumors and benign tumors

significantly associated with patient tumor history. On the other hand, there was no statistically significant difference in smoking history or alcohol consumption between the three groups. Similarly, there were no statistical significant differences associated with the size of tri-nucleotide repeat expansion, disease duration, type 2 diabetes or body-mass index.

Multivariable model comparing patients with any tumor to those without showed that female gender (OR 5.71, 95 % CI 2.90–11.22) and age at enrollment (OR 1.02, 95 % CI 1.00–1.05) were the only statistically significant factors associated with patient tumor history (Table 4). In analysis stratified on gender and malignancies only, having a history of thyroid disease resulted associated with increased risk of malignant tumors in women (OR 5.12, CI 95 % 1.35–19.37), whereas given the small number available in this analysis OR and CI were not calculable in men.

Discussion

Elevated cancer risk in DM1 patients is relatively new observation for which clinical and molecular risk factors are still unclear. In agreement with literature data [7–9], we also found a higher prevalence of malignant tumors among DM1 patients in comparison with our reference age-matched Italian population [14].

Additionally, we confirm the previously reported association between tumor history in patients with DM1 and both patient older age, and female gender [9, 10]. The association between patient age and tumor development may suggest that DM tumors develop in patients with milder phenotype; however, it is important to note that DM patients with severe phenotype suffer competing mortality that may obscure their true cancer risk. The effect of non-cancer competing mortality on cancer burden in DM patients has been discussed in a previous study [15]. Malignancies of the skin and thyroid, followed by that affecting the female reproductive organs (breast and ovary) were the most common in our cohort. While uterine fibroids in DM1 female patients showed a higher frequency (37.6 %) than expected based on published literature (25 %) [16].

Notably, tumor development in our DM1 population was not related to exposure to common lifestyle risk factors including alcohol consumption, smoking, and obesity, or to common clinical phenotype such as diabetes. Our findings together with results from cancer risk in relatives of DM patients [17] support a causal relationship between tumor development in DM1 patients and the underlying genetic defect of the disease.

Table 2 Malignant and benign tumors in 255 myotonic dystrophy 1 patients

	Total[a]			Male			Female		
	Malignant tumors	Benign tumors	Total	Malignant tumors	Benign tumors	Total	Malignant tumors	Benign tumors	Total
Uterus	1	41	42	0	0	0	1	41	42
Skin	6	2	8	3	2	5	3	0	3
Thyroid	4	1	5	1	1	2	3	0	3
Ovary	2	2	4	0	0	0	2	2	4
Breast	2	1	3	0	0	0	2	1	3
Meningiomas	0	2	2	0	0	0	0	2	2
Parotid gland	0	3	3	0	1	1	0	2	2
Angioma	0	1	1	0	1	1	0	0	0
Bone	0	1	1	0	0	0	0	1	1
Colon	0	1	1	0	1	1	0	0	0
Gallbladder	0	1	1	0	0	0	0	1	1
Lipoma	0	1	1	0	1	1	0	0	0
Liver	0	1	1	0	1	1	0	0	0
Lung	1	0	1	1	0	1	0	0	0
Lymphoma	1	0	1	0	0	0	1	0	1
Multiple myeloma	1	0	1	0	0	0	1	0	1
Kidney	1	0	1	0	0	0	1	0	1
Thymus gland	0	1	1	0	1	1	0	0	0
Total	19	59	78	5	9	14	14	50	64

[a] 19 malignant tumours in 17 patients and 59 benign tumors in 54 patients

Table 3 Clinical, molecular and demographic features of 255 myotonic dystrophy 1 patients, with and with tumor by selected covariates

	Without tumor (n = 192)	Benign tumors (n = 46)	Malignant tumors (n = 17)[a]	p value
Female	62 (32.3 %)	35 (76.1 %)	12 (70.6 %)	<0.001[b,c]
Age (years)	44.4 (±14.0)	48.2 (±10.1)	50.6 (±12.9)	<0.05
Body-mass index	25.4 (±4.2)	26.7 (±7.7)	25.4 (±5.2)	0.96
Smoking status				
Never smoker	110 (58.2 %)	22 (48.9 %)	10 (58.8 %)	0.52
Ever smoker	79 (41.8 %)	26 (51.1 %)	7 (41.2 %)	
Alcohol consumption				
Never drinker	89 (47.1 %)	23 (50.0 %)	5 (29.4 %)	0.32
Ever drinker	100 (52.9 %)	23 (50.0 %)	12 (70.6 %)	
Clinical features of DM1				
History of diabetes	17 (9.0 %)	5 (11.1 %)	1 (5.9 %)	0.86
History of thyroid disorder	35 (18.4 %)	15 (34.1 %)	8 (47.1 %)	<0.01[b]
Disease duration (years)	23.3 (±12.5)	25.1 (±13.3)	22.1 (±10.8)	0.75
Class of CTG expansion				
E1	32 (18.5 %)	8 (19.1 %)	4 (25.0 %)	0.41
E2	74 (42.8 %)	13 (30.9 %)	8 (50.0 %)	
E3	45 (26.0 %)	12 (28.6 %)	4 (25.0 %)	
E4	22 (12.7 %)	9 (21.4 %)	0 (0.0 %)	

Values are expressed as mean (standard deviation) or percentage

[a] 7 patients with one malignant tumor and one benign tumor, and one patient with two malignant tumors and one benign tumor, were included in malignant tumors group

[b] Significant difference between patients without tumor and patients with malignant tumor

[c] Significant difference between patients without tumor and patients with benign tumor

Similar to previous reports [9, 10], we did not find an association between leukocyte n(CTG) repeat size or disease duration and tumor development in our cohort. The lack of correlation between neoplasm development and n(CTG) repeat size is not surprising, since, except for age at onset of symptoms, the correlations between leukocyte repeat size and disease severity are not highly robust possibly due to the somatic mosaicism in DM1 patients [18, 19]. In this regard, the comparison between tumor and normal tissues from the same DM1 patients may clarify the contribution of somatic instability in the pathogenesis of tumors in DM1.

In our cohort, few cases of pilomatricoma ($n = 2$) were observed; however, pilomatricoma was the most common tumor in male patients. It has been proposed that CUGBP or MBNL1 dysregulation occurring in DM1 tissues might affect also Wnt signalling and regulation of beta catenin contributing to skin tumors, and possibly others, in myotonic dystrophies [20]. Our data did not support the possibility that aberrant expression of the insulin receptor (IR), with predominant expression of the IR-A isoform documented in DM1 tissues [21] could also play a role in tumor development in DM1 patients, since we found no association between patient history of diabetes and neoplasms. IR isoform is emerging as an important mechanism of normal and cancer stem cell and is a feature of several malignancies [22].

Our observation of a significant association between thyroid diseases (multinodular, non-toxic goiter) and malignant tumors in DM1 female patients is novel and may be of clinical importance, although it needs to be further confirmed by a larger study. A possible explanation for this finding could be represented by dysregulation of specific miRNAs recently documented in DM1 [23]. Such dysregulation has been associated with the pathogenesis of several neoplasms [24], including thyroid tumors [25]. Alternatively, the association between thyroid disorders and malignancies affecting the female reproductive organs could be related to the known endocrine system dysfunction in DM1 patients [1, 2]. Indeed, the endocrine dysfunction occurring in DM1 might cause imbalances in sex hormones, known risk factors for tumors affecting reproductive tissues [26–28]. So far, the only study extensively assessing endocrine function in a cohort of DM1 patients [29], including 48 women, documented hyperprolactine in only 2 % of female patients, whereas studies of the gonadal abnormalities in women were difficult to interpret because of the menarche cycle, and because testing of FSH, LH and estrogens was done at different stages of the female cycle [30]. Increased lifetime exposure to estrogens might also

Table 4 Odds ratio (95 % CI) for tumor (n=63) by demographic, clinical, and molecular features of 255 myotonic dystrophy 1 patients

	OR (95 % CI)	OR adjusted (95 % CI)
Gender		
Men	1.00	1.00
Women	6.16 (3.24–11.71)	5.71 (2.90–11.22)
Age (years)	1.02 (1.00–1.05)	1.02 (1.00–1.05)
Body-mass index	1.03 (0.98–1.09)	1.03 (0.96–1.09)
Smoking status		
Never	1.00	1.00
Ever	1.30 (0.73–2.32)	1.60 (0.81–3.16)
Alcohol consumption		
Never	1.00	1.00
Ever	1.11 (0.63–1.97)	1.78 (0.89–3.53)
Clinical features of DM1		
History of diabetes		
No	1.00	1.00
Yes	1.09 (0.41–2.90)	0.61 (0.19–1.99)
History of thyroid disorder		
No	1.00	1.00
Yes	2.68 (1.42–5.06)	1.66 (0.82–3.32)
Disease duration (years)	1.01 (0.98–1.03)	0.98 (0.96–1.01)
Class of CTG expansion		
E1	1.00	1.00
E2	0.76 (0.33–1.72)	0.81 (0.32–2.07)
E3	0.95 (0.39–2.27)	0.86 (0.32–2.29)
E4	1.09 (0.39–3.03)	0.77 (0.25–2.43)

OR adjusted by gender, age and history of thyroid disorder

arise in DM1 women from a lower delivery rate [28], related to reduced fertility likely due to a poorer ovarian reserve rather than hypogonadism [29]. Finally, age at menarche, oral contraceptive use and polycystic ovary might also be responsible of increased lifetime exposure to estrogens [26–28]. Thus, for future epidemiologic studies, an assessment of the above-mentioned factors is essential to elucidate their role in tumorigenesis of reproductive tissues in DM1 women.

In interpreting the results, we acknowledge some limitations in our study design. First, we were unable to directly compare cancer incidence in our cohort to that of the general Italian population since national cancer registry is still under establishment in Italy. Instead, we compared our results to published estimates of cancer prevalence in Italy.

Nevertheless, although performed on a small sample of patients compared with previous reports [7–9], our epidemiologic study included a detailed assessment of patients' exposure to most common life-style cancer risk factors, and medical record reviews for clinical and molecular information.

In conclusion, our findings confirm an increased risk of tumors in DM1, and rule out the possibility that this observation is confounded by life-habits. This reinforces a direct contribution of the underlying genetic defect in DM1 in tumor phenotype in those patients. We recommend including cancer clinical surveillance particularly among DM1 women to patient clinical care. This may be particularly important in those affected by thyroid disorders, an observation that needs to be confirmed. Additional systematic molecular and genetic studies regarding neoplasm in DM1 are needed to better understand the patho-mechanism of tumorigenesis and guide clinical care in those patients.

Acknowledgments The work of Dr. Emanuele Leoncini was supported by Fondazione Veronesi. Dr. Shahinaz Gadalla is supported by the intramural program of the National Cancer Institute, Bethesda, MA.

Compliance with ethical standards

Conflicts of interest The authors declare no conflict of interest.

Ethical standards The study was designed in accordance with the guidelines of the Ethical Committees of the Università Cattolica del Sacro Cuore, University of Tor Vergata, University La Sapienza and Azienda Ospedaliera S.Camillo Forlanini, Rome Italy, and in agreement with the Declaration of Helsinki.

References

1. Ashizawa T, Sarkar PS (2011) Myotonic dystrophy types 1 and 2. Handb Clin Neurol 101:193–237
2. PS Harper (2001) Myotonic Dystrophy, 3rd edn. London
3. Cantwell AR Jr, Reed WB (1965) Myotonia atrophica and multiple calcifying epithelioma of Malherbe. Acta Derm Venereol 45:387–390
4. Street ML, Rogers RS 3rd (1991) Multiple pilomatricomas and myotonic dystrophy. J Dermatol Surg Oncol 17:728–730
5. Laredo Ortiz C, Munoz Romero F, Mallent Anon J, Domenech Miro E, Tafalla Pena M (1997) Multiple pilomatrixomas associated with Steinert disease. An Med Interna 14:409–411
6. Barberio E, Nino M, Dente V, Delfino M (2002) Guess what! Multiple pilomatricomas and Steiner disease. Eur J Dermatol 12:293–294
7. Gadalla SM, Lund M, Pfeiffer RM, Gørtz S, Mueller CM, Moxley RT 3rd, Kristinsson SY, Björkholm M, Shebl FM, Hilbert JE, Landgren O, Wohlfahrt J, Melbye M, Greene MH (2011) Cancer risk among patients with myotonic muscular dystrophy. JAMA 306:2480–2486
8. Win AK, Perattur PG, Pulido JS, Pulido CM, Lindor NM (2012) Increased cancer risks in myotonic dystrophy. Mayo Clin Proc 87:130–135
9. Mohamed S, Pruna L, Kaminsky P (2013) Increasing risk of tumors in myotonic dystrophy type 1. Presse Med 42:281–284
10. Das M, Moxley RT 3rd, Hilbert JE, Martens WB, Letren L, Greene MH, Gadalla SM (2012) Correlates of tumor development in patients with myotonic dystrophy. J Neurol 259:2161–2166
11. Gennarelli M, Pavoni M, Amicucci P, Novelli G, Dallapiccola B (1998) A single polymerase chain reaction-based protocol for detecting normal and expanded alleles in myotonic dystrophy. Diagn Mol Pathol 7:135–137
12. Modoni A, Silvestri G, Pomponi MG, Mangiola F, Tonali PA, Marra C (2004) Characterization of the pattern of cognitive impairment in myotonic dystrophy type 1. Arch Neurol 61:1943–1947
13. [No authors listed] New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). The International Myotonic Dystrophy Consortium (IDMC) (2000) Neurology 54:1218-21
14. AIRTUM Working group (2011) Italian cancer figures, report 2011: survival of cancer patients in Italy. Epidemiol Prev 35:1–200
15. Gadalla SM, Pfeiffer RM, Kristinsson SY, Björkholm M, Hilbert JE, Moxley RT 3rd, Landgren O, Greene MH (2013) Quantifying cancer absolute risk and cancer mortality in the presence of competing events after a myotonic dystrophy diagnosis. PLoS ONE 8:e79851
16. Okolo S (2008) Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 22:571–588
17. Lund M, Diaz LJ, Gørtz S, Feenstra B, Duno M, Juncker I, Eiberg H, Vissing J, Wohlfahrt J, Melbye M (2014) Risk of cancer in relatives of patients with myotonic dystrophy: a population-based cohort study. Eur J Neurol 21:1192–1197
18. Udd B, Krahe R (2012) The myotonic dystrophies: molecular, clinical, and therapeutic challenges. Lancet Neurol 11:891–905
19. Thornton CA (2014) Myotonic dystrophy. Neurol Clin 32:705–719
20. Mueller CM, Hilbert JE, Martens W, Thornton CA, Moxley RT 3rd, Greene MH (2009) Hypothesis: neoplasms in myotonic dystrophy. Cancer Causes Control 20:2009–2020
21. Santoro M, Masciullo M, Bonvissuto D, Bianchi ML, Michetti F, Silvestri G (2013) Alternative splicing of human insulin receptor gene (INSR) in type I and type II skeletal muscle fibers of patients with myotonic dystrophy type 1 and type 2. Mol Cell Biochem 380:259–265
22. Belfiore A, Malaguarnera R (2011) Insulin receptor and cancer. Endocr Relat Cancer 18:R125–R147
23. Perbellini R, Greco S, Sarra-Ferraris G, Cardani R, Capogrossi MC, Meola G, Martelli F (2011) Dysregulation and cellular mislocalization of specific miRNAs in myotonic dystrophy type 1. Neuromuscul Disord 21:81–88
24. Cheng Q, Yi B, Wang A, Jiang X (2013) Exploring and exploiting the fundamental role of microRNAs in tumor pathogenesis. Onco Targets Ther 6:1675–1684
25. Pallante P, Battista S, Pierantoni GM, Fusco A (2014) Deregulation of microRNA expression in thyroid neoplasias. Nat Rev Endocrinol 10:88–101
26. Schuler S, Ponnath M, Engel J, Ortmann O (2013) Ovarian epithelial tumors and reproductive factors:a systematic review. Arch Gynecol Obstet 287:1187–1204
27. Anderson KN, Schwab RB, Martinez ME (2014) Reproductive risk factors and breast cancer subtypes: a review of the literature. Breast Cancer Res Treat 144:1–10
28. Kim JJ, Chapman-Davis E (2010) Role of progesterone in endometrial cancer. Semin Reprod Med 28:81–90
29. Ørngreen MC, Arlien-Søborg P, Duno M, Hertz JM, Vissing J (2012) Endocrine function in 97 patients with myotonic dystrophy type 1. J Neurol 259:912–920
30. Srebnik N, Margalioth EJ, Rabinowitz R, Varshaver I, Altarescu G, Renbaum P, Levi-Lahad E, Weintraub A, Eldar-Geva T (2014) Ovarian reserve and PGD treatment outcome in women with myotonic dystrophy. Reprod Biomed Online 29:94–101