HHS Public Access

Author manuscript

Eur J Neurol. Author manuscript; available in PMC 2018 May 01.

Published in final edited form as:

Eur J Neurol. 2017 May ; 24(5): 713–718. doi:10.1111/ene.13276.

Pigmentation Phenotype, Photosensitivity, and Skin Neoplasms in Patients with Myotonic Dystrophy

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Abstract

Background—Recent studies have suggested a possible excess risk of skin neoplasms in patients with myotonic dystrophy (DM). Risk factors related to this observation have not been defined.

Method—We collected information regarding personal history of skin tumors, pigmentation phenotype, and skin reaction to sun exposure from 266 DM patients who were enrolled in the US NIH National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members.

Results—Seventy-seven subjects reported having skin tumors that were either benign (n=31), malignant (n=32), or both (n=14). Female gender (OR=2.27, 95%CI=1.02–5.05, p=0.04), older age (OR=1.10, 95%CI=1.05–1.16, p<0.001), and DM1 subtype (OR=3.42, 95%CI=1.27–9.26, p=0.02) were associated with a malignant skin tumor. The association between malignant skin tumors and known risk factors [light eye color (OR=1.62, 95%CI=0.78–3.39, p=0.20); light skin complexion (OR=1.31, 95% CI=0.63–2.73, p=0.48), moderate/extensive face freckles (OR=1.47, 95% CI=0.50–4.34, p=0.49)] were modest. Strong, but not statistically significant, associations were noted with sunburn reactions when exposed to sunlight (OR=4.28, 95%CI=0.91–19.95, p=0.06, and 2.19, 95%CI=0.67–7.09, p=0.19 for sunburns with and without blistering, respectively).

Conclusions—Although our study was limited by small sample size, the risk factors for malignant skin tumors in DM strongly resemble the general population. We recommend that DM patients adhere to sun exposure protective behavior.

Keywords

Myotonic dystrophy; cancer; skin; risk factors; repeat expansion size

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CONFLICTS OF INTEREST

None of the manuscript authors has conflict of interest to disclose

INTRODUCTION

Myotonic dystrophy (Dystrophia Myotonica; DM) is an autosomal dominant multisystem disorder characterized by progressive muscle weakness and myotonia [1]. The disease is caused by a trinucleotide repeat (CTG) expansion in the 3′-untranslated region of the Dystrophia Myotonica Protein Kinase (*DMPK*) gene in DM type 1, [2] or a tetranucleotide (CCTG) repeat expansion in intron1 of the CCHC-type Zinc Finger Nucleic Acid Binding Protein (*CNBP*) gene in DM type 2.[3, 4] Case reports have suggested that DM patients are at increased risk of certain benign and malignant tumors, the most coming being pilomatricoma - a rare, benign, calcifying skin tumor derived from hair matrix cells.[5] Recent studies have also found that skin cancers are the most common malignant neoplasm in DM1 patients.[6, 7] Several registry-based epidemiological studies of cancer risk in DM patients suggest that DM patients may be at higher risks of both melanoma (SIR/RR ranging between 2.05, and 7.1)[8–10] and non-melanoma (SIR=2.1, 95%CI=1.2–3.4)[8] skin cancers than the general population. A prospective study has revealed a higher frequency of dysplastic nevi (4.4% vs. 1.9%), and melanoma skin cancer (3.3% vs. 0%) in patients with DM1 than controls.[11] The nuclear sequestration of muscleblind-like protein1 (*MBNL1*) that occurs in DM may play a role in the development of skin cancer in those patients.[5, 12] Previous studies of potential tumor risk factors in DM patients found no association between tumor history and patient lifestyle factors, such, as smoking and obesity.[6, 7] However, studies analyzing specific risk factors for skin cancers, such as, skin complexion, eye color, and skin response to sun exposure are limited. Understanding the contribution of such factors in DM-related cancers may facilitate the development of clinical and preventive guidelines, and guide molecular research of cancer in DM.

MATERIALS & METHODS

Data Collection and Study Participants

This study is part of a larger effort to understand factors that contribute to the development of benign and malignant neoplasms in DM patients. We mailed a cancer history and risk factor questionnaire to 850 genetically and/or clinically confirmed DM patients who were enrolled in the NIH supported, US National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members (US DM Registry). Detailed information regarding the US DM Registry is available elsewhere.[7, 13] After 3 mailing attempts, 280 patients (219 DM1 and 61 DM2) responded to all or parts of the questionnaires. We excluded 14 patients who did not respond to either the tumor history questionnaire or the sun exposure questions.

The study was approved by the Ethics Committees of the University of Rochester, and the National Institutes of Health Office of Human Subjects Research and was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. All patients included in this study gave their informed consent to participate.

Study Outcome and Exposure Variables

The study outcome was self-reported skin neoplasms (benign or malignant). DM patients were asked to report the type of the tumor(s) (pilomatricoma, other benign, basal or squamous cell carcinoma, or melanoma), and the age and year of diagnosis for each. We asked patients about their skin complexion (light, medium, or dark), natural eye color (blue, green, hazel, light brown, dark brown, or other), skin response to sun exposure (blistering sunburn, sunburn without blister, mild sunburn that becomes a tan, a tan without sunburn, or no change) and the degree of face freckling (absent, mild, moderate, or extensive). Patient demographic and clinical information were available through the US DM Registry database.

Statistical Analysis

For univariate analyses, we used the chi-square test for categorical variables, and Student's t-test for continuous variables. We compared patient characteristics by skin tumor status (none, benign only, malignant with or without benign). For multivariable analyses, we used multinomial logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of benign and malignant skin tumors by patient demographic variables, clinical factors, and cutaneous phenotype data.

For the final analyses, skin complexion was categorized into light *vs.* medium/dark; eye color was categorized into light (blue, grey, or green) and dark (hazel, light or dark brown); response to sun exposure was categorized into sunburn with blistering, sunburn no blistering, and tan without sunburn/no change; and degree of face freckling was categorized into none/mild *vs.* moderate/extensive.

All models were adjusted for gender, age at study enrollment, age at DM diagnosis, and DM subtype (DM1 or DM2). All analyses were performed using SPSS Version 21.0 (IBM Corp. Armonk, NY)

RESULTS

Patient Characteristics

The study included 266 DM patients (age range=18–83 years), of whom 194 had adult-onset DM1, 60 had DM2, and 12 had congenital DM1; almost all (95.9%) were white. Compared with non-responders, those patients were older at DM diagnosis (mean=37.8±15.9 years *vs.* 30.7±16.7 years, $p<0.001$), more likely to be females (57.9% *vs.* 50.6%, $p=0.03$), or to have had a history of tumor (27.1% *vs.* 16.1%, $p<0.001$). For study participants, almost all (95.9%) were white. For patients who responded, the median CTG -repeat size for the subset of DM1 with available genetic test results (n=110; 50.9%) was 325 (range=42–1700) [Normal range for DMPK gene CTG size is 5–37 repeats]. Among DM2 patients (n=27; 45%), the median CCTG-repeat size was 12,000 (range=149–156,006) [Normal range for CNBP gene CCTG size is 10–33 repeats].

Skin Neoplasms by Patient Demographics and Clinical Characteristics

Overall, 77 patients reported having benign or malignant skin tumors (31 had benign tumors only, 32 malignant tumors only, and 14 had both). The frequencies of reporting benign

(12.1% and 10%, respectively) or malignant (18.4 and 13.3%, respectively) skin tumors were similar for DM1 and DM2 patients. Among patients with any type of benign skin tumor (n=45), 12 patients (26.7%) had pilomatricoma (mean age at diagnosis=46.6±16.8 years). Other benign skin tumors reported by 2 or more patients included actinic keratosis/keratosis (n=2), atypical/precancerous lesion, not otherwise specified (n=2), lipoma (n=3), and cysts (n=2). For malignant skin tumors, the mean age at diagnosis was 57±11.8. Twenty-five patients (54.3%) had basal cell carcinoma, 5 patients (10.9%) had squamous cell carcinoma, 3 patients (6.5%) had melanoma, and 10 patients (21.7%) had at least 2 different cancer types. The type of reported skin cancer was not specified in 3 patients. Table 1 summarizes patient demographic and clinical characteristics by history of skin tumor. Statistically significant differences by tumor status (none, benign only, malignant +/− benign) were noted for patient gender ($p<0.01$), age at DM diagnosis ($p=0.004$), and age at study enrollment ($p<0.001$).

Multivariable analysis showed that men were more likely to develop benign skin tumors (OR=2.37, 95%CI=1.07–5.26, p=0.03), while women were more likely to develop malignant tumors (OR=2.27, 95%CI=1.02–5.05, p=0.04). No other factors were associated with reporting benign skin tumors. Yet, DM1 subtype (OR =3.42, 95%CI=1.27–9.26, p=0.02), and older age (OR=1.10, 95%CI=1.05–1.16, $p<0.001$) were associated with history of malignant skin tumors (Table 2).

Pigmentation Phenotype & Photosensitivity and Risk of Skin Neoplasms

More than half (56%) of the DM patients reported having light skin complexion, 42.5% reported light eye color (blue, grey, or green), 10% reported having extensive face freckling, and 9.4% reported developing blistering sunburn when exposed to sunlight.

No statistically significant differences were noted in the odds of benign or malignant skin tumor by eye color (p=0.27), skin complexion (p=0.78), degree of face freckling (p=0.09), or skin reaction to sun exposure (p=0.58) (Table 3).

Multivariable analyses of the combined populations of DM1 and DM2 patients suggested a possible association between history of malignant skin neoplasm and having light eye color (OR=1.62, 95%CI=0.78–3.39, p=0.20), light skin complexion (OR=1.31, 95%CI=0.63–2.73, p=0.48), moderate or extensive face freckles (OR=1.47, 95%CI=0.50–4.34, p=0.49), or developing blistering sunburns (OR=4.28, 95%CI=0.91–19.95, p=0.06) or sunburns without blistering (OR=2.19, 95%CI=0.67–7.09, p=0.19) when exposed to sunlight. Yet, no associations were noted with benign tumors, except possible association with developing blistering sunburns upon sun exposure (OR=2.53, 95%CI=0.57–11.26, p=0.22) (Table 3)

DISCUSSION

Several reports have suggested that DM patients are at high risk of skin neoplasms. Understanding risk factors associated with such observations may guide prevention and screening strategies. The current study showed a higher risk of malignant skin tumors in female patients and in subjects with the DM1 disease subtype. Our findings related to skin phenotype in relation to cancer risk were inconclusive, in part due to our small sample size.

Pigmentation phenotype and skin response to sun exposure are risk factors for both melanoma and non-melanoma skin cancers.[14–17] Our results from this study of US NIH National DM Registry participants show modest (although not statistically significant) positive associations between having a history of skin cancer and light eye color (OR=1.62), light skin complexion (OR=1.31), face freckles (OR=1.47), or sunburns (OR= 4.28 for sunburns with blistering, and 2.19 for sunburns without blistering). A larger study is needed to confirm our observations. Because of the strong effect size associated with sunburns, we recommend advising DM patients to use sunscreen and other sun-protective behaviors according to general population guidelines. Examples of skin cancer educational materials can be found on the American Academy of Dermatology website (https://www.aad.org/public/spot-skin-cancer/programs/screenings/30-years-of-skin-cancer-awareness)

Our study showed a clear gender difference between the risk of benign and malignant skin tumors, with higher risks of malignant skin neoplasms in female DM patients. This finding differs from the known higher susceptibility of sporadic skin cancers in men.[18–20] Previous DM studies showed that women were more likely to develop cancers (the absolute risk of all cancer, excluding non-melanoma skin, by age 60 years=13.3% *vs.* 4.4% in female and male DM patients, respectively).[21] This apparent gender difference in skin cancer risk in DM patients is not yet understood. The higher mortality rate in men with DM compared with women[22–24] may contribute to the observed cancer-related sex difference because many cancers are associated with age. Alternatively, a specific biological mechanism (yet to be identified) may be involved. A recent large study identified gender as a modifying factor of DM phenotypic variation.[25] In that study, men with DM were more likely to develop a severe muscle phenotype, pulmonary or cardiac complications, while women were more likely to develop cataract, dysphagia, and thyroid disease. Cancers were not part of that report.

Similar to previous findings in DM-related brain cancers,[26] skin tumor in DM patients appears to be a disease of adulthood (minimum age at pilomatricoma diagnosis=20 years, at other benign skin tumors=29 years, and at skin cancer diagnosis=30 years), which was not related to age at DM diagnosis (a proxy measure for DM severity). Additionally, there were no associations between benign or malignant skin tumors and the nucleotide repeat size in blood samples. Previous studies[6, 7, 9] of cancer risk in DM patients reported similar observations, but those results, as well as ours, are limited by small sample sizes.

Previous work using data collected from 915 DM patients from the NIH supported US National Registry of Myotonic Dystrophy Patients and Family Members found that patients with DM1 were more likely to develop tumors than those with DM2.[7] In the current report we show that this is also true for skin neoplasms, particularly for malignant tumors [(OR=3.4); the OR for benign tumors in patients with DM1 compared with DM2 was 1.62]. Previous studies have suggested that the tumor profile in DM patients may be different by disease subtype. [7,10] Understanding the similarities and differences between cancer phenotype in DM1 and DM2 is important in guiding patient clinical management.

The strengths of this study include its relatively large sample size of well-characterized DM patients, from whom detailed risk factor information had been collected. The study was

limited by our inability to objectively validate the self-reported skin neoplasms. Self-reporting of personal cancer history has been deemed valid by multiple studies, but accuracy of diagnosis by cancer type is variable, with better reporting for the more common cancers. [27–29] This may or may not be true for the validity of the self-reporting of benign tumors. In addition, our questionnaire response rate was suboptimal (280/850=33%) in part, perhaps, as a consequence of the cognitive dysfunction that is part of the DM phenotype. Future questionnaire studies targeting DM patients should be designed with this potential respondent limitation in mind.

In conclusion, our data indicated that female DM patients and those with DM1 were more likely to develop skin cancer than male patients, and those with DM2. Patients need to seek dermatologic consultation when suspicious lesions are detected because the vast majority of these lesions are readily curable with local therapy. Despite the lack of statistical significance, our data show that the direction and magnitude of associations between cutaneous phenotype and risk of malignant skin tumors in DM patients are similar to those reported in the general population. Therefore, we recommend that DM patients adhere to standard sun exposure protective behavior including frequent, liberal use of sunscreens, sun protective clothing, and diligent avoidance of sunburn. Future studies are needed to investigate potential mechanisms that may contribute to an increased risk of skin cancer in patients with DM.

Acknowledgments

We thank the patients for their participation.

FUNDING

This study was supported in-part by the Intramural Research Program of the National Cancer Institute, USA. The US National Registry of Myotonic Dystrophy Patients and Family Members is supported through the National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Neurological Disorders and Stroke (NIH Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Center grant #U54-NS048843 at the University of Rochester and NIH contracts #N01-AR-5-2274 and #NO1-AR-0-2250), and the National Center for Research Resources and the National Center for Advancing Translational Sciences (NIH: UL1 RR024160).

References

1. Thornton CA. Myotonic dystrophy. Neurol Clin. 2014; 32:705–719. viii. [PubMed: 25037086]
2. Fu YH, Pizzuti A, Fenwick RG Jr, et al. An unstable triplet repeat in a gene related to myotonic muscular dystrophy. Science. 1992; 255:1256–1258. [PubMed: 1546326]
3. Ranum LP, Rasmussen PF, Benzow KA, Koob MD, Day JW. Genetic mapping of a second myotonic dystrophy locus. Nat Genet. 1998; 19:196–198. [PubMed: 9620781]
4. Liquori CL, Ricker K, Moseley ML, et al. Myotonic dystrophy type 2 caused by a CCTG expansion in intron 1 of ZNF9. Science. 2001; 293:864–867. [PubMed: 11486088]
5. Mueller CM, Hilbert JE, Martens W, Thornton CA, Moxley RT 3rd, Greene MH. Hypothesis: neoplasms in myotonic dystrophy. Cancer Causes Control. 2009; 20:2009–2020. [PubMed: 19642006]
6. Bianchi ML, Leoncini E, Masciullo M, et al. Increased risk of tumor in DM1 is not related to exposure to common lifestyle risk factors. J Neurol. 2016; 263:492–498. [PubMed: 26739382]
7. Das M, Moxley RT 3rd, Hilbert JE, et al. Correlates of tumor development in patients with myotonic dystrophy. J Neurol. 2012; 259:2161–2166. [PubMed: 22619053]

8. Gadalla SM, Lund M, Pfeiffer RM, et al. Cancer risk among patients with myotonic muscular dystrophy. JAMA. 2011; 306:2480–2486. [PubMed: 22166607]
9. Mohamed S, Pruna L, Kaminsky P. Increasing risk of tumors in myotonic dystrophy type 1. Presse Med. 2013; 42:e281–284. [PubMed: 23477718]
10. Win AK, Perattur PG, Pulido JS, Pulido CM, Lindor NM. Increased cancer risks in myotonic dystrophy. Mayo Clin Proc. 2012; 87:130–135. [PubMed: 22237010]
11. Zampetti A, Silvestri G, Manco S, et al. Dysplastic nevi, cutaneous melanoma, and other skin neoplasms in patients with myotonic dystrophy type 1: a cross-sectional study. J Am Acad Dermatol. 2015; 72:85–91. [PubMed: 25440959]
12. 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. ArchDermatolRes. 2010; 302:169–170.
13. Hilbert JE, Kissel JT, Luebbe EA, et al. If you build a rare disease registry, will they enroll and will they use it? Methods and data from the National Registry of Myotonic Dystrophy (DM) and Facioscapulohumeral Muscular Dystrophy (FSHD). ContempClinTrials. 2012; 33:302–311.
14. Kricker A, Armstrong BK, English DR, Heenan PJ. Pigmentary and cutaneous risk factors for non-melanocytic skin cancer–a case-control study. Int J Cancer. 1991; 48:650–662. [PubMed: 2071226]
15. English DR, Armstrong BK, Kricker A, Winter MG, Heenan PJ, Randell PL. Case-control study of sun exposure and squamous cell carcinoma of the skin. Int J Cancer. 1998; 77:347–353. [PubMed: 9663594]
16. Naldi L, DiLandro A, D'Avanzo B, Parazzini F. Host-related and environmental risk factors for cutaneous basal cell carcinoma: evidence from an Italian case-control study. J Am Acad Dermatol. 2000; 42:446–452. [PubMed: 10688715]
17. Gandini S, Sera F, Cattaruzza MS, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005; 41:45–60. [PubMed: 15617990]
18. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7–30. [PubMed: 26742998]
19. de Vries E, Micallef R, Brewster DH, et al. Population-based estimates of the occurrence of multiple vs first primary basal cell carcinomas in 4 European regions. Arch Dermatol. 2012; 148:347–354. [PubMed: 22431775]
20. Madan V, Lear JT, Szeimies RM. Non-melanoma skin cancer. Lancet. 2010; 375:673–685. [PubMed: 20171403]
21. Gadalla SM, Pfeiffer RM, Kristinsson SY, et al. Quantifying cancer absolute risk and cancer mortality in the presence of competing events after a myotonic dystrophy diagnosis. PLoS One. 2013; 8:e79851. [PubMed: 24236163]
22. de Die-Smulders CE, Howeler CJ, Thijs C, et al. Age and causes of death in adult-onset myotonic dystrophy. Brain. 1998; 121(Pt 8):1557–1563. [PubMed: 9712016]
23. Groh WJ, Groh MR, Shen C, Monckton DG, Bodkin CL, Pascuzzi RM. Survival and CTG repeat expansion in adults with myotonic dystrophy type 1. Muscle Nerve. 2011; 43:648–651. [PubMed: 21484823]
24. Mathieu J, Allard P, Potvin L, Prevost C, Begin P. A 10-year study of mortality in a cohort of patients with myotonic dystrophy. Neurology. 1999; 52:1658–1662. [PubMed: 10331695]
25. Dogan C, De Antonio M, Hamroun D, et al. Gender as a Modifying Factor Influencing Myotonic Dystrophy Type 1 Phenotype Severity and Mortality: A Nationwide Multiple Databases Cross-Sectional Observational Study. PLoS One. 2016; 11:e0148264. [PubMed: 26849574]
26. Gadalla SM, Pfeiffer RM, Kristinsson SY, Bjorkholm M, Landgren O, Greene MH. Brain tumors in patients with myotonic dystrophy: a population-based study. Eur J Neurol. 2016; 23:542–547. [PubMed: 26508558]
27. Bergmann MM, Calle EE, Mervis CA, Miracle-McMahill HL, Thun MJ, Heath CW. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. Am J Epidemiol. 1998; 147:556–562. [PubMed: 9521182]

28. Desai MM, Bruce ML, Desai RA, Druss BG. Validity of self-reported cancer history: a comparison of health interview data and cancer registry records. Am J Epidemiol. 2001; 153:299–306. [PubMed: 11157418]

29. Klein BE, Lee KE, Moss SE, Trentham-Dietz A, Klein R. Self- and registry-reported cancer in a population-based longitudinal study. WMJ. 2010; 109:261–266. [PubMed: 21066931]

Table 1

Patient Characteristics by history of skin tumors

Variable	No Tumors N=189	Benign only N=31	Malignant Tumors N=46	P-value
	N (%)[a]			
Gender				<0.01
M	80 (69.6%)	20 (17.4%)	15 (13.0%)	
F	109 (72.2%)	11 (7.3%)	31 (20.5%)	
DM subtype				0.54
DM1	143 (69.4)	25 (12.1)	38 (18.4)	
DM2	46 (76.7)	6 (10.0)	8 (13.3)	
Education				0.16
High School or less	54 (79.4)	8 (11.8)	6 (8.8)	
College or equivalent	86 (72.9)	10 (8.5)	22 (18.6)	
Graduate school	43 (59.7)	12 (16.7)	17 (23.6)	
	Mean+/−SD			
Age at DM diagnosis	36.3+/−16.3	40.0+/−16.0	45.0+/−13.4	0.004
Age at study enrolment	51.0+/−13.2	53.4+/−12.8	62.8+/−10.2	<0.001
CTG repeat size in DM1	408.9+/−339.7	397.0+/−275	268+/−243	0.30
CCTG repeat size in DM2	17591.1+/−30544.1	11220+/−395.98	12350+/−353.6	0.94

[a]Row percentage

Table 2

The adjusted odds ratios (OR) of having benign or malignant skin tumors by selected demographics and clinical factors in patients with DM

Variables		OR (95% CI)[a]	P-value
Benign Tumors	Age at enrollment	0.99 (0.95–1.05)	0.94
	Age at DM diagnosis	1.02 (0.98–1.07)	0.34
	Female *vs.* male	0.42 (0.19–0.94)	0.03
	DM1 *vs.* DM2	1.62 (0.57–4.63)	0.37
Malignant Tumors	Age at enrollment	1.10 (1.05–1.16)	<0.001
	Age at DM diagnosis	0.99 (0.96–1.03)	0.80
	Female *vs.* male	2.27 (1.02–5.05)	0.04
	DM1 *vs.* DM2	3.42 (1.27–9.26)	0.02

[a]Odds ratio and 95% confidence interval; the model included age at enrollment, age at DM diagnosis, gender, and DM subtype (DM1 or DM2).

Table 3

Risk of skin tumors by pigmentation phenotype, and skin response to sun exposure

	None	Benign only		Malignant tumors	
	N (%)	N (%)	OR (95% CI)[a] P-value	N (%)	OR[a] (95% CI) P-value
Eye color					
Light	76 (39.6)	13 (41.9)	0.98 (0.48–2.16) 0.96	25 (54.3)	1.62 (0.77–3.39) 0.20
Dark	108 (60.4)	18 (58.1)	Reference	21 (45.6)	Ref
Skin complexion					
Light	108 (56.2)	16 (51.6)	0.89 (0.40–1.98) 0.78	27 (58.7)	1.31 (0.63–2.73)
Medium/dark	78 (43.8)	15 (48.4)	Reference	19 (41.3)	Ref
Face Freckles					
Moderate/severe	23 (12.6)	0 (0)	N/A	7 (15.6)	1.47 (0.50–4.34) 0.49
None or mild	159 (87.4)	31 (100)	Reference	38 (84.4)	Ref
Skin reaction to sun exposure					
Sun burn+/−Blistering	73 (38.0)	12(38.7)	2.53 (0.57–11.26) 0.22	23 (50)	4.27 (0.91–19.95) 0.06
Mild burn that becomes a tan	78 (40.6)	13 (41.9)	0.91 (0.33–2.52) 0.86	19 (41.3)	2.19 (0.67–7.10) 0.19
Tan with no sunburn or no skin change	31 (16.1)	6 (19.4)	Reference	4 (8.7)	Ref

[a]Odds ratio and 95% confidence interval; models are adjusted for age at enrolment, age at DM diagnosis, gender, and DM subtype.