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**Risk of skin cancer among patients with myotonic dystrophy type 1 based on  
Primary care physician data from the United Kingdom Clinical Practice Research Datalink**

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**Short title:** Risk of skin cancer in DM1

**Key words:** Myotonic dystrophy, cancer, skin, basal cell carcinoma, melanoma, non-melanoma

**Abbreviations:**

BCC	Basal cell carcinoma
CPRD	Clinical Practice Research Datalink
DM1	Myotonic dystrophy type 1
DMPK	Dystrophia myotonica protein kinase
HES	Hospital Episode Statistics
HR	Hazard ratio
IMD	Indices of Multiple Deprivation
MBLN-1	Muscleblind like splicing regulator 1
NMSC	Non-melanoma skin cancers
SCC	Squamous cell carcinoma
SD	Standard deviation
SIR	Standardized incidence ratio
95% CI	95% confidence interval

**Novelty and Impact:**

Patients with myotonic dystrophy type 1 (DM1), an inherited tri-nucleotide repeat disorder, are at high risk of certain cancers. However, risk of skin cancers in those patients was not comprehensively evaluated. Using data from the UK Clinical Practice Datalink, we showed that DM1 patients are at high risk of basal cell carcinoma (HR=5.8,  $p<0.0001$ ), and possibly melanoma (HR=2.4,  $p=0.24$ ). The findings provide evidence that skin cancer is part of the DM phenotype.

**Article category:** Cancer Epidemiology

**Disclaimer:** The results were presented at the 2017 International Conference on Pharmacoepidemiology & Therapeutic Risk Management.

## ABSTRACT

Myotonic dystrophy type 1 (DM1) is an inherited multisystem neuromuscular disorder caused by a CTG trinucleotide repeat expansion in the *DMPK* gene. Recent evidence documents that DM1 patients have an increased risk of certain cancers, but whether skin cancer risks are elevated is unclear. Using the U.K. Clinical Practice Research Datalink (CPRD), we identified 1,061 DM1 patients and 15,119 DM1-free individuals matched on gender, birth year ( $\pm 2$  years), attending practice, and registration year ( $\pm 1$  year). We calculated the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of DM1 diagnosis with skin cancer risk using Cox proportional hazards models, for all skin cancers combined and by histological subtype. Follow-up started at the latest of the age at practice registration, DM1 diagnosis/control selection or January 1st 1988, and ended at the earliest of the age at first skin cancer diagnosis, death, transfer out of the practice, last date of data collection or the end of the CPRD record (October 31, 2016). During a median follow-up of 3.6 years, 35 DM1 patients and 108 matched DM1-free individuals developed a skin cancer. DM1 patients had an increased risk of skin cancer overall (HR=5.44, 95% CI=3.33-8.89,  $p < .0001$ ), and basal cell carcinoma (BCC) (HR=5.78, 95% CI=3.36-9.92,  $p < .0001$ ). Risks did not differ by gender, or age at DM1 diagnosis ( $P$ -heterogeneity  $> 0.5$ ). Our data confirm suggested associations between DM1 and skin neoplasms with the highest risk seen for BCC. Patients are advised to minimize ultraviolet light exposure and seek medical advice for suspicious lesions.

## INTRODUCTION

Myotonic dystrophy type 1 (*dystrophia myotonica*, DM1, also called Steinert's disease) is an autosomal dominant multisystem disorder caused by unstable (CTG)<sub>n</sub> trinucleotide repeat expansion in the 3' noncoding region of the dystrophia myotonica protein kinase (*DMPK*) gene on chromosome 19q13.3<sup>1-3</sup>. The prevalence of DM1 ranges from 0.5/100,000 in Taiwan<sup>4</sup> to 1/550 in Northeastern Quebec<sup>5</sup>; the estimate for Europe ranges from 6.8/100,000 to 36.2/100,000<sup>6-8</sup>. Myotonia and muscle weakness are the main clinical presentations of DM1. Other prevalent manifestations include posterior subcapsular cataracts, cardiac conduction abnormalities, central nervous system dysfunctions, and endocrine abnormalities<sup>9</sup>. Recently, large epidemiological studies indicated that cancer is part of the DM phenotype<sup>10-12</sup>, but lacked the information required to adequately assess the risk of skin cancers.

Case reports and small case series have suggested a possible link between DM and both pilomatricoma -a rare, benign, calcifying cutaneous tumor arising from the hair matrix,<sup>13</sup> and basal cell carcinoma (BCC)<sup>13-15</sup>. Large DM registry studies from the U.S., Italy, and the U.K. have shown that cancers of the skin are the most common cancer in DM1 patients (n=32/781, 6/255, and 4/231, respectively)<sup>16-18</sup>; however, comparisons of risk with that in the general population were not available. Two small studies from Italy comparing dermatological findings of DM1 patients with controls showed significantly higher frequencies of pilomatricoma<sup>19</sup>, dysplastic nevi<sup>19, 20</sup>, and melanoma<sup>19</sup> in DM1 patients, but found contradictory results with BCC<sup>19, 20</sup>. Similar results for pilomatricoma were reported in a single Spanish center study using patient medical records<sup>21</sup>. No significant BCC prevalence difference between DM1 patients and controls was noted; however, DM1 patients developed BCC at a younger age than controls.

In the current study, we used computerized primary care physician records from the U.K. to evaluate the risk of skin cancers (overall and by subtype) in a large cohort of patients with DM1 compared with age and sex-matched DM1-free controls.

## **METHODS**

### **Data sources**

The U.K. Clinical Practice Research Datalink (CPRD) is one of the world's largest anonymized longitudinal databases of electronic primary care medical records, derived from more than 4 million active patients and 650 general care practices around the U.K.<sup>22</sup> CPRD started in June 1987, first known as Value Added Medical Products (VAMP) Research Databank, but earlier data are available. The database includes demographic information, clinical diagnoses, test results, immunization and referral records, selected lifestyle factors, and prescription records. Clinical diagnoses are recorded using Read codes, a unique clinical terms coding system used in the U.K. National Health Service (<https://data.gov.uk/dataset/uk-read-code>). All patients in CPRD are linkable to practice level Indices of Multiple Deprivation (IMD, a proxy measure for socioeconomic measure), and approximately 57% of the participating CPRD practices in the U.K. and 75% of CPRD practices located in England are linkable to the Hospital Episode Statistics (HES) inpatient records database from April 1997 to February 2016<sup>23</sup>. Patients attending CPRD participating practices were found to be representative of the U.K. population with regard to age and sex<sup>22</sup>.

## **Study population**

From the October 2016 CPRD data release, we identified all patients with a DM1 diagnosis (n=1,061) using Read codes F392011: Steinert's disease, and F392000: Dystrophia myotonica (Steinert's disease). For each DM1 patient, we randomly selected up to 20 individuals from the pool of DM1-free individuals registered in the same practice and who were alive at the index date (defined as the date at 1<sup>st</sup> DM1 record for patients diagnosed after their date of practice registration, or the date of practice registration, if diagnosed prior to enrollment). DM1 patients and DM1-free individuals were additionally matched on gender, year of birth ( $\pm 2$  years), and practice registration year ( $\pm 1$  year); the total number of DM1-free individuals was 15,119.

**Figure 1** provides a flow chart of participant selection.

The study protocol was reviewed and approved by the CPRD Independent Scientific Advisory Committee (ISAC; protocol 16\_005RA2R). Our use of CPRD database was approved by the National Institutes of Health Office of Human Subject Research Protection.

## **Skin cancer outcomes**

The outcome of interest was the first skin cancer (all types combined and stratified by histological subtypes) occurring during follow-up. In the main analysis, we used Read codes (available in **Supplemental Table 1**) to identify skin cancers from primary care physicians' records. Primary care physicians in the UK are the center of health care delivery; they treat, refer, and follow-up, therefore their records capture patient information through the health care continuum. In a sensitivity analysis, we used ICD-10 codes C43 (malignant melanoma of skin), and C44 (other malignant neoplasms of skin) to identify skin cancers from hospital records using HES database. This analysis included the subset of patients who are linkable to HES.



## **Statistical analysis**

We used Cox proportional hazard regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of having DM1 with the first diagnosis of skin cancer occurring during follow-up, overall and by subtype. Skin cancer risk in DM1 patients was compared with that in matched DM1-free subjects. The proportional hazards assumption was evaluated using Schoenfeld residuals, and no significant violation was observed.

We used age as the time scale for all analyses. Follow-up started at the latest of age at index date, or January 1st 1988 (after the start of CPRD database). For the sensitivity analysis using the HES database, we started follow-up at the latest of age at index date or April 1<sup>st</sup> 1997 (after the start of HES data linkage). Late entry into the cohort was accounted for in PROC PHREG procedure, SAS 9.3<sup>24</sup>. Follow-up ended at the earliest of age at 1<sup>st</sup> record of any skin cancer, death, transfer out of the practice, last data collection, or end of database record (for CPRD: October 31, 2016, for HES: February 29, 2016). For subtype analysis, skin cancer diagnosis other than the subtype of interest were treated as censored (i.e. follow-up ended at 1<sup>st</sup> skin cancer of any type).

The matched design of DM1 and DM1-free subjects was accommodated by stratifying the baseline hazard function on the matching ID. The models were additionally adjusted for yearly average number of clinic visits, calculated as the total number of clinical events (maximum one per day) after start of follow-up until 1 year prior to the skin cancer or censor date, divided by the number of years of follow-up.

The analysis was further stratified by gender (male, female), patient registration year at the clinic (<1991, 1991-2000, >2000), age at DM1 diagnosis (<30, ≥30), and geographical region of the practice (north, central, south). We tested the difference of the magnitude of the associations

between DM1 and skin cancer across categories using a Wald test, computed as the difference of the estimates squared divided by the sum of the variances, as the estimates for different strata are independent.

To assess the robustness of our findings, we conducted several sensitivity analyses. First, we repeated the analysis restricted to DM1 patients (and their matched controls) who had their 1<sup>st</sup> DM1 event recorded at the current clinic after the start of CPRD (on or after January 1<sup>st</sup> 1988; N=538 and 6,849 for DM1 patients and DM1-free subjects, respectively). This would restrict the analysis to patients with prospectively recorded diagnoses and thus bring greater certainty about the exact date of first diagnosis of DM1 and skin cancer. Second, we repeated the analysis including only patients with first DM1 record after the date CPRD identified the practice recording to be “up-to-standard”<sup>22</sup> (N=403 and 4,849 for DM1 patients and DM1-free subjects, respectively). Again, this would ensure better data quality. Third, we excluded individuals with skin cancer records before the start of study follow-up (N=21 DM1, and 73 DM1-free). Fourth, we restricted the analysis to a subset of patients who were linked to the HES database (N=573 and 7,614 for DM1 patients and DM1-free subjects with unique HES ID, respectively), in which skin cancer outcomes were identified only from the hospital records. Lastly, we restricted the analysis to DM1 patients with unique HES ID who had DM diagnosis records in both HES (ICD-10 code G71.1) and CPRD (N=374) and their 5,435 DM1-free matched subjects.

All p values were two-sided with statistical significance defined as  $p < 0.05$ . All analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.3.3.

## RESULTS

### Characteristics of DM1 patients and matched DM1-free subjects

DM1 patients were first diagnosed between 1944 and 2016, at a mean age of 32.7 years (SD=18.6). The mean age at the start of follow-up was 38.1 years (SD=17.0) for DM1 patients and 35.6 years (SD=16.6) for the matched DM1-free subjects. The median follow-up time was 5.4 years for DM1 patients and 3.5 years for the DM1-free individuals. Approximately 51% of both cohorts were female, and 80% were from England. More clinic visits were noted for the DM1 patients than the DM1-free cohort (mean number of annual visits=10.4 (SD=12.2) and 5.0 (SD=8.4), respectively). The characteristics of DM1 patients and matched DM1-free subjects are presented in **Table 1**.

### The association between DM1 and skin cancer risk

During 90,455 person-years of follow-up, 35 DM1 and 108 matched DM1-free subjects developed skin cancer, corresponding to crude incidence rates of 434.6 and 131.1 per 100,000 person-years among DM1 and DM1-free subjects, respectively. The mean (SD) age at 1<sup>st</sup> skin cancer diagnosis during follow-up in DM1 patients was 57.3 years (11.0), *versus* 63.3 years (13.0) in the DM1-free subjects.

In multivariable analysis, DM1 patients had a statistically significantly increased risk of all skin cancers combined compared with their matched DM1-free subjects (HR=5.44, 95% CI=3.33-8.89,  $p<0.0001$ ). The risk was highest for BCC (HR=5.78, 95% CI=3.36-9.92,  $p<0.0001$ ).

Although not statistically significant, DM1 patients had an approximately two-fold increase in melanoma risk (HR=2.40, 95% CI=0.56-10.31,  $p=0.24$ ). No squamous cell carcinomas (SCCs) were reported in DM1 patients. Similar results were observed when excluding patients with skin

cancer diagnoses within the first 6 months of the start of follow-up (potential prevalent cancer cases)(**Table 2**).

In stratified analyses, there was no evidence of differences in the magnitude of risk of overall skin cancer or BCC by gender (p-heterogeneity=0.99 and 0.56, respectively) or geographical region (p-heterogeneity=0.98 and 0.88, respectively). We also found no evidence of heterogeneity in the risk of all skin cancer combined and BCC by registration year to the practice (p-heterogeneity=0.91 and 0.72, respectively), or age at DM1 diagnosis (p-heterogeneity=0.40 and 0.50, respectively) (**Table 3**).

Results from sensitivity analyses were consistent with those of the main analysis. Specifically, similar results were observed from models restricted to: 1) patients diagnosed with DM1 after the start of CPRD (HR=5.61, 95% CI=3.01-10.45 for all skin cancers combined, and HR=6.19, 95% CI=3.18-12.08 for BCC), 2) patients diagnosed with DM1 after the clinic “up-to-standard” date (HR=5.08, 95% CI=2.45-10.53 for skin cancer combined, and HR=5.84, 95% CI=2.71-12.57 for BCC only). In analysis restricted to patients with no prior history of skin cancer, the observed risk estimates slightly attenuated for both all skin cancer combined (HR=4.87, 95% CI=2.85-8.29), and for BCC (HR=4.86, 95% CI=2.68-8.82).

In subgroup analysis using HES database (573 DM1 and 7,614 DM1-free), having DM1 was associated with an approximately four-fold excess in the risk of non-melanoma skin cancers (NMSC) (HR=3.78, 95% CI=1.44-9.90, p=0.01). These data also suggested a possible risk for melanoma skin cancer, however not statistically significant (HR=3.38, 95% CI=0.25-46.17, p=0.36).

When restricting the analysis to patients with DM codes in both HES and CPRD (N=374) and their matched DM1-free cohort (N=5,435), DM1 patients showed an approximately seven-fold excess in the risk of all skin cancer combined (HR=7.41, 95% CI=3.31-16.59) and that of BCC (HR=6.71, 95% CI=2.86-15.76). The risk estimates were attenuated when the analyses were repeated in DM1 cases whose diagnosis were identified from one source (CPRD only) (for all skin cancer combined: HR=4.54, 95% CI=2.33-8.85, for BCC: HR=5.34, 95% CI=2.51-11.39).

## **DISCUSSION**

In this large cohort of 1,061 patients with DM1 and 15,119 DM1-free matched individuals, we used electronic primary care health records to quantify the risk of skin cancer in those patients. We showed that DM1 patients are at a particularly high risk for basal cell carcinoma, and possibly melanoma, but no evidence of an excess risk of squamous cell carcinoma.

DM1 patients in this study had a 6-fold increase in the risk of BCC compared with matched DM1-free individuals. On the contrary, none of the DM1 patients had records of squamous cell carcinoma compared with 6 cases in the DM1-free individuals, suggesting that DM1 patients may be at a lower risk of cutaneous SCC. Because NMSC, particularly BCC is generally underreported in cancer registries<sup>25,26</sup>, adequate comparative studies were not available with the exception of data from Denmark which suggested an excess risk of NMSC in DM patients (standardized incidence ratio (SIR)=2.08; 95% CI=1.2-3.4)<sup>10</sup>. Results related to risk of SCC need to be interpreted with caution since a validation study of primary care recording for cutaneous SCC in the UK has shown that physicians tend to use non-organ specific codes for recording cutaneous SCC (53%)<sup>27</sup>. Here, we used skin-specific SCC codes to ensure organ specificity, therefore it is possible that SCC cases were underascertained. Yet, concerns related to possible

differential misclassification bias are lessened since both DM1 patients and DM1-free subjects were selected from the same practice and therefore similar reporting patterns are expected. Our estimated risk for melanoma in this study agrees with that previously reported in other DM population- and clinic-based studies (SIR=2.3 in Scandinavian patients<sup>10</sup>, 1.7 in patients from the Basque, Spain<sup>12</sup>, and 2.05 in a US cohort<sup>11</sup>); none of these risk estimates reached statistical significance.

The molecular mechanism underlying skin tumorigenesis in DM1 patients is still unknown, but several mechanisms have been hypothesized, including aberrant  $\beta$ -catenin accumulation via the Wnt/ $\beta$ -catenin signaling pathway<sup>13</sup>, and depletion/ malfunction of the RNA binding protein-muscleblind like splicing regulator 1 (*MBLN-1*)<sup>14</sup>. A recent study suggested a role for Vitamin D homeostasis in DM skin abnormalities including dysplastic nevi; an inverse correlation between Vitamin D level and the presence of dysplastic nevi was observed<sup>20</sup>.

Our study showed no gender differences in the relative risks of BCC (HR=5.09 vs 7.01, in men and women), or melanoma (3.27 vs 1.97, in men and women) in DM1 patients. This finding is similar to those previously reported in DM1 patients from Sweden and Denmark for cancers other than that of the reproductive organs<sup>10</sup>. Yet, this contrasts skin cancer statistics from the U.K. general population, in which men are at higher risk of BCC<sup>28</sup>, and women are at higher risk of melanoma<sup>29</sup>. Other known skin cancer risk factors include older age, fair skin color, light eye color and a tendency to burn on sun exposure<sup>30-33</sup>. In our study, DM1 patients appeared to develop melanoma skin cancer at a relatively early age. All melanoma cases among DM1 patients were diagnosed at <65 years of age (median age=43.8 years) versus 70% in the controls. In the U.K., about 50% of melanoma cases are diagnosed among people aged  $\geq 65$  years<sup>34</sup>. The

age difference at skin cancer diagnosis was less clear in BCC, in which DM1 patients were diagnosed at a slightly younger age than DM1-free controls (58.5 vs. 62.3) . It is possible that the early age at skin cancer diagnosis in DM1 patients represents ascertainment bias due to the frequent and close medical surveillance they experience in the course of their care for a serious, multisystem disorder.

Our data showed no significant association between age at DM1 diagnosis (an indicator of disease severity) and skin cancer risk. This is similar to our previous finding in DM-related brain cancer, in which no association between risk and age at DM diagnosis was observed<sup>35</sup>. Similarly, tumor development in DM patients did not correlate with the size of nucleotide repeat measured in patient blood (another proxy of disease severity) in several studies<sup>12, 16, 17, 19</sup>.

The strengths of the current study include its relatively large sample size, longitudinal design that ensured the identification of incident cancer cases, and the use of matched comparison cohort design. The ascertainment of cancer diagnosis from clinical records minimized the possible recall bias often associated with survey studies. The use of data from the primary health care setting allowed the inclusion of the full spectrum of DM1 cases, minimizing selection bias associated with identifying patients only from hospital records or tertiary care centers.

Additionally, and in contrast to most cancer registries, the CPRD data captured NMSC.

Several limitations existed including our inability to directly adjust for the known skin cancer risk factors such as sun exposure and cutaneous phenotype, which are not uniformly captured with UK primary care records. Suggestive associations between risk of skin malignancies and pigmentation phenotype or reaction to sun exposure have been observed in a previous DM study<sup>36</sup>. Given the close medical attention DM1 patients receive, it is likely that our observed

association is affected by detection bias. To minimize this possibility, we adjusted our models for the yearly average number of doctor visits. Additionally, it is possible that DM1 diagnosis in CPRD may not be accurately recorded. We investigated DM1 diagnosis validity in 516 DM1 patients with any HES record, and found that 374 of them had DM1 records in both sources. The stronger associations we observed when restricting the analysis to those with DM1 diagnosis in both sources suggest that our results are valid and that possible bias that may be associated with DM1 misclassification is pulling the results toward the null.

In conclusion, our study showed that patients with DM1 are at increased risk of basal cell carcinoma and possibly melanoma. It is important that DM1 patients adhere to sun protective behaviors, minimizing exposure to ultraviolet light, and to seek medical advice if suspicious skin lesions appeared. Molecular studies aiming at elucidating the biological pathways involved in DM1 skin carcinogenesis are warranted, since it may provide novel insights into our understanding of DM-related carcinogenesis, in general.



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## **Conflict of Interest**

None to disclose

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## TABLES

**Table 1. Study cohort characteristics**

Characteristics	DM1 patients	DM1-free subjects
	(N=1,061)	(N=15,119)
	N (%)	N (%)
Follow-up (person-years)	8054.3	82400.4
Age at start of follow-up, year		
≤20	155 (14.6%)	2446 (16.2%)
>20, ≤30	207 (19.5%)	3609 (23.9%)
>30, ≤40	210 (19.8%)	3068 (20.3%)
>40, ≤50	206 (19.4%)	2729 (18.0%)
>50	283 (26.7%)	3267 (21.6%)
Age at 1 <sup>st</sup> DM diagnosis in CPRD, year		
≤15	191 (18.0%)	
>15, ≤30	286 (27.0%)	
>30, ≤45	285 (26.9%)	
>45, ≤60	225 (21.2%)	
>60	74 (7.0%)	
Gender		
Male	520 (49.0%)	7350 (48.6%)
Female	541 (51.0%)	7769 (51.4%)
Year at registration to the practice		
Before 1991	336 (31.7%)	4239 (28.0%)
1991-2000	293 (27.6%)	4689 (31.0%)
After 2000	432 (40.7%)	6191 (40.9%)
Practice located in England	844 (79.5%)	12346 (81.7%)
UK Region of included practices <sup>1</sup>		
North	370 (34.9%)	5079 (33.6%)
Central	340 (32.0%)	4701 (31.1%)
South	351 (33.1%)	5339 (35.3%)
Socioeconomic status <sup>2</sup> based on practice location, quintile		
1 (Most affluent)	158 (14.9%)	2206 (14.6%)
2	181 (17.1%)	2467 (16.3%)
3	196 (18.5%)	2795 (18.5%)
4	221 (20.8%)	3175 (21.0%)
5	305 (28.7%)	4476 (29.6%)
Average Annual number of practice visit <sup>3</sup>		

0-1	187 (17.6%)	6049 (40.0%)
>1, ≤5	224 (21.1%)	4295 (28.4%)
>5	650 (61.3%)	4775 (31.6%)

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<sup>1</sup> North: North West England, Yorkshire & The Humber, Northern Ireland, North East England, and Scotland

Central: East of England, Wales, West Midlands, and East Midlands

South: South West England, South East Coast, South Central England and London

<sup>2</sup> Using practice level Indices of Multiple Deprivation data

<sup>3</sup> Average number of clinic visit/year after the start date until 1 year prior to the end of follow-up

**Table 2. Risk of skin cancers, overall and by histological subtype in patients with DM1.**

Outcome	All Patients (N=16,180)			Excluding individuals with skin cancer event occurred within 6 months of start of follow-up (N=16,171)		
	N event (crude incident rate <sup>1</sup> )	HR <sup>2</sup> (95% CI)	P	N event (crude incident rate <sup>1</sup> )	HR <sup>2</sup> (95% CI)	p
<b>1<sup>st</sup> skin cancer<sup>3</sup></b>						
DM1-free subjects <sup>4</sup>	108 (131.07)	1.00 (reference)		100(121.36)	1.00 (reference)	
DM1 patients	35 (434.55)	5.44 (3.33-8.89)	<.0001	34 (422.14)	5.81 (3.52-9.59)	<.0001
<b>Melanoma</b>						
DM1-free subjects	20 (24.27)	1.00 (reference)		20 (24.27)	1.00 (reference)	
DM1 patients	<5 (37.25)	2.40 (0.56-10.31)	0.24	<5 (37.25)	2.40 (0.56-10.31)	0.24
<b>Basal cell carcinoma</b>						
DM1-free subjects	80 (97.09)	1.00 (reference)		73 (88.59)	1.00 (reference)	
DM1 patients	30 (372.47)	5.78 (3.36-9.92)	<.0001	29 (360.06)	6.48 (3.71-11.34)	<.0001

<sup>1</sup> per 100,000 person-years.

<sup>2</sup> Models were stratified on matched set, and adjusted for average number of clinic visit/year after the start date until 1 year prior to the end of follow-up.

<sup>3</sup> In addition to the melanoma and BCC cases in the table, there were 6 SCC (all in DM1-free subjects), and <5 skin cancer, not otherwise specified in all patients; person-year of follow-up=82400 for DM1-free subjects, and 8054 for DM1 patients in analysis of all patients, and 82399 and 8054, respectively in analysis excluding cases within first 6 months of follow-up

<sup>4</sup> DM1-free individuals were matched to DM1 patients on gender, birth year ( $\pm 2$  years), attending practice, and registration year ( $\pm 1$  year).

**Table 3. The association between skin cancer and DM1 stratified by selected characteristics.**

Characteristics	1 <sup>st</sup> skin cancer (all subtypes) <sup>1</sup>				Basal cell carcinoma			
	DM1 patients	DM1-free subjects <sup>2</sup>	HR <sup>3</sup> (95% CI)	P	DM1 patients	DM1-free subjects <sup>2</sup>	HR <sup>3</sup> (95% CI)	p
	N event (crude incident rate <sup>4</sup> )				N event (crude incident rate <sup>4</sup> )			
<b>Gender</b>								
Male	18 (451.96)	63 (151.81)	5.54 (2.86-10.73)	<.0001	15 (376.63)	46 (110.84)	5.09 (2.45-10.54)	<.0001
Female	17 (417.53)	45 (110.02)	5.51 (2.64-11.49)	<.0001	15 (368.41)	34 (83.13)	7.01 (3.10-15.90)	<.0001
	P <sub>heterogeneity</sub>		0.99		P <sub>heterogeneity</sub>		0.56	
<b>Registration year</b>								
Before 1991	18 (471.86)	55 (145.05)	5.06 (2.63-9.74)	<.0001	16 (419.43)	41 (108.13)	5.94 (2.93-12.05)	<.0001
1991-2000	9 (374.18)	29 (103.08)	6.39 (2.21-18.54)	<.001	8 (332.61)	21 (74.64)	7.43 (2.19-25.27)	<.01
After 2000	8 (436.12)	24 (146.80)	4.68 (1.58-13.87)	0.01	6 (327.09)	18 (110.10)	3.75 (1.12-12.57)	0.03
	P <sub>heterogeneity</sub>		0.91		P <sub>heterogeneity</sub>		0.72	
<b>Age at 1<sup>st</sup> DM diagnosis</b>								
< 30	5 (122.06)	12 (29.95)	3.02 (0.68-13.39)	0.15	<5 (97.64)	8 (19.97)	3.22 (0.51-20.46)	0.22
≥ 30	30 (758.00)	96 (226.77)	5.94 (3.53-9.98)	<.0001	26 (656.94)	72 (170.08)	6.25 (3.55-11.01)	<.0001
	P <sub>heterogeneity</sub>		0.40		P <sub>heterogeneity</sub>		0.50	
<b>Region<sup>5</sup></b>								
North	12 (398.23)	43 (145.66)	5.18 (2.21-12.12)	<.001	11 (365.04)	35 (118.56)	6.65 (2.68-16.55)	<.0001
Central	11 (434.89)	32 (132.46)	5.49 (2.36-12.75)	<.0001	8 (316.28)	22 (91.07)	4.77 (1.80-12.63)	<.01
South	12 (477.80)	33 (114.89)	5.81 (2.39-14.11)	<.001	11 (437.98)	23 (80.08)	5.98 (2.33-15.40)	<.001
	P <sub>heterogeneity</sub>		0.98		P <sub>heterogeneity</sub>		0.88	

<sup>1</sup> Includes melanoma, basal cell carcinoma, squamous cell carcinoma of skin and other skin cancer, not otherwise specified.

<sup>2</sup> DM1 patients and DM1-free subjects were matched on gender, birth year (±2 years), attending practice, and registration year (±1 year).

<sup>3</sup> Models were stratified on matched set, and adjusted for average number of clinic visit/year after the start date to 1 year prior to the end of follow-up.

<sup>4</sup> per 100,000 person-years.

<sup>5</sup> North: North West England, Yorkshire & The Humber, Northern Ireland, North East England, and Scotland

Central: East of England, Wales, West Midlands, and East Midlands

South: South West England, South East Coast, South Central England and London



**Figure 1. Flow chart of study participants**

