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Genetic variants in telomere-maintaining genes and skin cancer risk

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Abstract

Telomere-related genes play an important role in maintaining the integrity of the telomeric structure that protects chromosome ends, and telomere dysfunction may lead to tumorigenesis. We evaluated the associations between 39 SNPs, including 38 tag-SNPs in telomere-related genes (*TERT*, *TRF1*, *TRF2*, *TNKS2*, and *POT1*) and one SNP (rs401681) in the *TERT-CLPTMIL* locus which has been identified as a susceptibility locus to skin cancer in the previous GWAS, and the risk of skin cancer in a case-control study of Caucasians nested within the Nurses' Health Study (NHS) among 218 melanoma cases, 285 squamous cell carcinoma (SCC) cases, 300 basal cell carcinoma (BCC) cases, and 870 controls. Of the 39 SNPs evaluated, ten showed a nominal significant association with the risk of at least one type of skin cancer. After correction for multiple testing within each gene, two SNPs in the *TERT* gene (rs2853676 and rs2242652) and one SNP in the *TRF1* gene (rs2981096) showed significant associations with the risk of melanoma. Also, the SNP rs401681 in the *TERT-CLPTMIL* locus was replicated for the association with melanoma risk. The additive odds ratio (OR) (95% confidence interval (95% CI)) of these four SNPs (rs2853676[T], rs2242652[A], rs2981096[G], and rs401681[C]) for the risk of melanoma was 1.43 (1.14–1.81), 1.50 (1.14–1.98), 1.87 (1.19–2.91), and 0.73 (0.59–0.91), respectively. Moreover, we found that the rs401681[C] was associated with shorter relative telomere length (p for trend, 0.05). We did not observe significant associations for SCC or BCC risk. Our study provides evidence for the contribution of genetic variants in the telomere-maintaining genes to melanoma susceptibility.

Keywords

SNP; Telomere-maintaining gene; Skin cancer

Introduction

Telomeres are distinctive structures capping both ends of linear eukaryotic chromosomes. Human telomeres consist of long hexameric (TTAGGG) $_n$ repeats, which are associated with a number of telomere-related proteins. The repeating sequences of telomeres comprise

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double-strand DNA with a G-rich single-strand 3' overhang end (Wai 2004). A minimal length of telomeric DNA, the integrity of the 3' overhang, and regulation of telomere-related proteins are important in maintaining the proper telomeric structure that protects chromosomes from end-to-end fusion, nucleolytic decay, and atypical recombination (Blasco 2003; Lundblad and Szostak 1989). At each cell division, the telomeres shorten by 30–200 bp due in part to failed replication of 3' telomeric DNA by DNA polymerases (Wai 2004).

UVB, a DNA-damaging agent and major risk factor for skin cancer, is known to target telomeric repeats. UV-damaged telomeric DNA is less well repaired than transcriptionally active regions, resulting in substantial loss of terminal telomere repeats or telomere shortening (Kruk et al. 1995). Telomere disruption evokes multiple cellular responses: entering replicative senescence, triggering apoptosis, or undergoing malignant transformation (Campisi et al. 2001; Chang and Harley 1995; Lundblad and Szostak 1989). The three major cell types of the epidermis (melanocytes, squamous keratinocytes, and basal keratinocytes) give rise to melanoma, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC), respectively. A previous study reported by our group showed that shorter telomere length was associated with a decreased risk of melanoma and an increased risk of BCC; there was no clear association between telomere length and SCC risk (Han et al. 2009).

Telomere length is maintained by telomerase, a ribonucleoprotein that adds the telomeric repeat sequence directly to the single-strand 3' overhang. As the catalytic subunit of telomerase, telomere reverse transcriptase (TERT) is the most important determinant in the regulation of telomerase expression (Blasco 2003; Bodnar et al. 1998). Two major telomere-related proteins, telomeric repeat binding factor 1 (TRF1) and telomeric repeat binding factor 2 (TRF2), directly bind to the double-strand region of telomere (Broccoli et al. 1997; Chong et al. 1995). The tankyrase (TNKS) increases telomere length by inhibiting TRF1, a negative regulator of telomerase activity (Smith and de Lange 2000). Another major telomere-related protein, protection of telomeres 1 (POT1), binds specifically to the single-strand 3' overhang at the distal ends of telomeres (Baumann and Cech 2001). TRF2 and POT1 are particularly important for stabilizing the telomeric structure that protects chromosome ends (Baumann and Cech 2001; Greider 1999; Karlseder et al. 1999; van Steensel et al. 1998).

To follow up on our previous study of telomere length and skin cancer risk, we conducted a case-control study of Caucasians nested within the Nurses' Health Study (NHS) to evaluate associations between genetic variants in telomere-related genes (*TERT*, *TRF1*, *TRF2*, *TNKS2*, and *POT1*) and the risk of three most common skin cancer types (melanoma, SCC, and BCC).

Materials and Methods

Study population

The Nurses' Health Study (NHS) was established in 1976, when 121,700 female registered nurses between the ages of 30 and 55 residing in 11 larger U.S. states completed and returned the initial self-administered questionnaire on their medical histories and baseline health-related exposures, forming the basis for the NHS cohort. Updated information has been obtained by questionnaires every two years. Eligible cases in this study consisted of women with incident skin cancer from the subcohort who gave a blood specimen in 1989–1990 ($n = 32,826$), including SCC and BCC cases with a diagnosis any time after blood collection up to June 1, 1998 and melanoma cases up to June 1, 2000 with no previously diagnosed skin cancer. A common control series was randomly selected from participants

who gave a blood sample and were free of diagnosed skin cancer up to and including the questionnaire cycle during which the case was diagnosed. One or two controls were matched to each case by year of birth (± 1 year). All subjects were drawn from among the U.S. non-Hispanic Caucasian women in this study. The nested case-control study consisted of 218 incident melanoma cases, 285 incident SCC cases, a sample of 300 BCC cases from the large number of incident cases, and 870 age-matched controls. Among 870 controls, 838 were previously assayed for relative telomere length (Han et al. 2009).

We obtained information regarding skin cancer risk factors from the prospective biennial questionnaires and a retrospective supplementary questionnaire. Questions on natural hair color, childhood and adolescent tanning tendency, and childhood sunburn reaction were included in the 1982 prospective questionnaire. The total number of moles (and the number of palpably raised moles) on arms, natural skin color, and other sun exposure-related information were collected by the retrospective supplementary questionnaire in 2002.

Details of the endometrial case-control study nested within the NHS have been published previously (McGrath et al. 2008). Briefly, endometrial cases consisted of women with confirmed invasive endometrial cancer diagnosed anytime after cohort inception until June 1, 2004. Women who had not had a hysterectomy and were free of cancer were selected as controls. Controls were matched to cases according to age, menopausal status, postmenopausal hormone use, and biospecimen type. In addition to 838 skin cancer controls, we had 800 controls from the nested endometrial cancer case-control study that were successfully assayed for relative telomere length. In order to increase statistical power, we combined both 838 skin cancer controls and 800 endometrial cancer controls for the analyses of genetic variants in telomere-related genes and relative telomere length. The study protocols were approved by the Committee on Use of Human Subjects of the Brigham and Women's Hospital, Boston, MA.

Laboratory assays

Using the International HapMap project (www.HapMap.org), we identified single nucleotide polymorphisms (SNPs) that effectively cover our genes of interest. Some of these SNPs are in linkage disequilibrium; therefore, a more efficient set of tagging SNPs can be used to capture the same genetic variation (Haiman and Stram 2008). Using Haploview program version 3.12 and a minimum r^2 threshold of 0.8, we identified a set of 38 parsimonious tagging SNPs to capture genetic variation in each locus (introns and exons as well as 3 kb upstream of the start of transcription and 3 kb downstream of the end of transcription) of five genes including *TERT* (10), *TRF1* (8), *TRF2* (5), *TNKS2* (9), and *POT1* (6). We also genotyped a SNP rs401681 in the *TERT-CLPTMIL* locus, which has recently been associated with the risks of several cancer types including skin cancer (Rafnar et al. 2009). Information on these 39 SNPs is presented in Supplementary Table 1. We genotyped these SNPs using the TaqMan Open Array SNP genotyping platform (Biotrove, Woburn, MA) using 384-well format TaqMan assays. TaqMan® primers and probes were designed using Primer Express® Oligo Design software v2.0 (ABI PRISM). Laboratory personnel were blinded to case-control status, and 10% blinded quality control samples (duplicate samples) were inserted to validate genotyping procedures; concordance for the blinded quality control samples was 100%. Primers, probes, and conditions for genotyping assays are available upon request.

Relative average telomere length was measured in genomic DNA. We employed a version of the quantitative PCR telomere assay modified for use in a high-throughput 384-well format on the Applied Biosystems 7900HT PCR System, which has been previously described (Han et al. 2009).

Statistical methods

We used the χ^2 test to determine whether SNPs were in Hardy-Weinberg equilibrium within the control populations. We compared each skin cancer type with the common skin cancer control series to increase statistical power. We evaluated the association between each genotype and skin cancer risk using unconditional logistic regression. An additive model was used to calculate the p -value on skin cancer risk according to an ordinal coding for genotype (0, 1, or 2 copies of SNP minor allele). We used Dersimonian-Laird random-effects models to examine the associations of genetic variants in telomere-related genes with telomere length among the 1,638 controls that were successfully assayed for relative telomere length (838 skin cancer controls and 800 endometrial cancer controls). Furthermore, we calculated the Spearman's correlation coefficients to assess the correlations between genetic variants in the telomere-related genes and total number of moles (and the number of palpably raised moles) on arms among 870 skin cancer controls. Considering as outliers, women who reported more than 20 moles (or 10 palpably raised moles) on arms were excluded from the analyses. All statistical analyses were two-sided and carried out using SAS V9.1 (SAS Institute, Cary, NC).

Results and Discussion

The characteristics of cases and controls in the skin cancer nested case-control study are presented in Table 1. A detailed description was published previously (Han et al. 2006). In brief, at the beginning of the follow-up (at blood collection), the age of the women was between 43 and 68 years (mean age 58.7). The mean age at diagnosis of incident melanoma cases was 63.3 years, and that of SCC cases and BCC cases was 64.7 and 64.0 years, respectively. Risk factors for skin cancer included family history of skin cancer, sun exposure with a bathing suit, sunlamp use or tanning salon attendance, and lifetime sunburns. Melanoma cases were more likely to have a higher number of moles on the arms. Women in the West and South regions were more likely to be diagnosed with SCC or BCC compared with those in the Northeast. Across all three types of skin cancers, cases were more likely to have light pigmentary phenotypes, including lighter skin and hair color, lower tendency to tan, and increased tendency to burn. For endometrial cancer case-control study, the characteristics of cases and controls have been previously described (McGrath et al. 2008). The mean age of the women at diagnosis of endometrial cancer was 59.0 years. The characteristics of endometrial cancer controls used in this study are presented in Supplementary Table 2. All related information was obtained from the NHS prospective biennial questionnaires. Because endometrial cancer controls were also randomly selected among the women in the NHS who provided blood samples and were free of cancer at blood collection, the characteristics of endometrial cancer controls were similar with that of skin cancer controls.

Genotype distributions of the 39 SNPs evaluated in this study were in Hardy-Weinberg equilibrium within each control population. We evaluated the main effect of each polymorphism across three types of skin cancer. Of the 39 SNPs evaluated, ten showed a nominal significant association with at least one type of skin cancer (p -values <0.05) (Table 2). Trends remained nominally significant after additionally adjusting for skin cancer risk factors or telomere length (Table 2). After correction for multiple testing within each gene, two SNPs in the *TERT* gene (rs2853676 and rs2242652) (p -values $<0.05/10$ (10 SNPs in the *TERT* gene for each type of skin cancer) $=0.005$) and one SNP in the *TRF1* gene (rs2981096) (p -value $<0.05/8$ (8 SNPs in the *TRF1* gene for each type of skin cancer) $=0.0063$) showed significant associations with melanoma risk in age-adjusted models. Also, the SNP rs401681 in the *TERT-CLPTMIL* locus was replicated for the association with melanoma risk (p -value $=0.004$) (Table 2). The additive odds ratio (OR) (95% confidence interval (95% CI)) of these four SNPs (rs2853676[T], rs2242652[A], rs2981096[G], and

rs401681[C]) for the risk of melanoma was 1.43 (1.14–1.81), 1.50 (1.14–1.98), 1.87 (1.19–2.91), and 0.73 (0.59–0.91), respectively (Table 2). The ORs from co-dominant models were presented in Supplementary Table 3. When we further performed a multivariate analysis mutually adjusting for those three significant SNPs in or near the *TERT* gene, two SNPs (rs2853676 and rs401681) remained significant. The age-adjusted OR (95% CI) of rs2853676[T] and rs401681[C] for the risk of melanoma was 1.38 (1.06–1.80) and 0.75 (0.59–0.94), respectively. With these significance thresholds, we did not observe significant associations for BCC or SCC risk.

In our previous study, we observed a marginally significant association of shorter telomere length with a decreased risk of melanoma, but an increased risk of BCC (Han et al. 2009). In this study, for rs401681[C], we observed a decreased risk of melanoma and a non-significantly increased risk of BCC. When we further evaluated the association of the 39 tag-SNPs with relative telomere length among controls from both the skin cancer and endometrial cancer studies, we observed a suggestive positive relationship between rs401681[C] and shorter relative telomere length (p for trend, 0.05) (Supplementary Table 4). This is consistent with what would be expected based on the directions of the associations of rs401681[C] with melanoma and BCC risks. Additionally, our results are supported by a recent report by Rafnar et al. (Rafnar et al. 2009). The authors found significant association of rs401681[C] with a decreased risk of melanoma, but an increased risks of several cancer types (BCC, lung, bladder, prostate, and cervix cancer). The OR (95% CI) for melanoma and BCC risk was 0.88 (0.82–0.95) and 1.25 (1.18–1.34), respectively. In contrast, a recent study conducted by Pooley et al. reported that the SNP rs401681 was not associated with mean telomere length as well as the risks of multiple cancers including melanoma (Pooley et al.). We did not find any other SNPs associated with relative telomere length in our data set (Supplementary Table 4).

We previously reported a positive association between the number of moles on arms and telomere length ($p=0.003$) (Han et al. 2009). Similarly, Bataille et al. showed that mole counts and size were positively correlated with telomere length (Bataille et al. 2007). In this study, we assessed the association between the 39 tag-SNPs in the telomere-related genes and total number of moles (and the number of palpably raised moles) on arms among skin cancer controls. Two SNPs in the *TRF2* gene, rs153045 (p -values, 0.0003 and 0.0005) and rs251796 (p -values, 0.0009 and 0.002), showed significant associations with both total number of moles and the number of palpably raised moles on arms. For the other SNPs, we did not find significant associations (Supplementary Table 5).

In summary, we observed significant associations of two SNPs in the *TERT* gene (rs2853676 and rs2242652) and one SNP in the *TRF1* gene (rs2981096) with melanoma risk. Also, the rs401681[C] in the *TERT-CLPTMIL* locus was replicated for the inverse association with melanoma risk. Moreover, we found that the rs401681[C] was associated with shorter relative telomere length. *TERT* and *TRF1* play vital roles in the regulation of telomerase activity, and telomerase activity is crucial in the elongation of telomere length in tumor cells (Blasco 2003; Bodnar et al. 1998; Smith and de Lange 2000). It is plausible that telomere length plays a critical role in determining the fate of different types of cells in tumorigenesis (Han et al. 2009). Squamous keratinocytes have a low apoptotic threshold, making the apoptotic pathway the predominant protective mechanism (Nemes and Steinert 1999). In contrast to squamous keratinocytes, basal keratinocytes are less susceptible to apoptosis (Gilchrest et al. 1999). Compared to both the basal and squamous keratinocytes, melanocytes have a greater tendency to senescence in response to oncogenic stress, rather than undergoing apoptosis (Mooi and Peeper 2006). Shorter telomere length may limit the proliferation of melanocytic nevus (a potential precursor of melanoma) before entry into senescence (Bataille et al. 2007). Reduced proliferation capacity due to shorter telomere

length may be reflected in skin with fewer melanocytic nevi and reduced subsequent melanoma development.

Our data benefit from prospective study design in which a defined cohort was assembled, and incident cases were compared with non-cases (controls) in a nested case-control study. Selection bias was eliminated, as cases and controls were from well-characterized relatively homogeneous populations. Recall bias was also minimized, as host factor information was obtained prospectively. One potential limitation of this study is that some important genetic variants especially rare variants may not be covered by the tagging approach. Overall, our findings provide evidence for the contribution of genetic variants in the telomere-related genes to melanoma development among Caucasian women. Further functional characterization of these telomere-related SNPs would be helpful to interpret their associations with telomere length and skin cancer risk. The sample size of this study was modest, and additional studies are warranted to confirm the associations observed in the present study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

SCC	Squamous Cell Carcinoma
BCC	Basal Cell Carcinoma
OR	Odds Ratio
CI	Confidence Interval
UV	Ultraviolet

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Table 1

Characteristics of skin cancer cases and controls in the nested case-control study

Characteristic	Controls (n=870)	Melanoma (n=218)	SCC (n=285)	BCC (n=300)
Age at diagnosis, mean (SD)	64.5 (7.0)	63.3 (7.3)	64.7 (7.0)	64.0 (7.1)
Family history of skin cancer (%)	25.1	36.5	35.7	42.7
Highest quartile of sun exposure with a bathing suit (%)	33.4	53.3	46.1	42.6
Sunlamp use or tanning salon attendance (%)	10.0	19.2	14.3	14.7
Number of lifetime severe sunburns (mean)	5.4	9.6	7.8	8.2
Total number of moles on arms, mean (SD)	3.0 (4.5)	4.4 (5.6)	2.5 (4.3)	3.4 (4.9)
Number of palpably raised moles on arms, mean (SD)	1.0 (1.8)	1.8 (2.7)	1.1 (2.0)	1.2 (1.9)
Childhood tendency to tan (%)	48.0	38.8	42.7	45.0
Childhood tendency to burn (%)	33.0	49.8	51.0	52.0
Natural red or blonde hair color (%)	12.5	23.3	20.3	20.7
Natural fair skin color (%)	39.9	57.1	54.6	53.0
Geographic region at baseline (%)				
Northeast	55.2	58.0	51.7	49.3
Northcentral	23.4	16.9	17.1	20.3
West and South	21.4	25.1	31.1	30.3

SD, standard deviation.

Table 2

Associations between selected SNPs in telomere-related genes and skin cancer risk

SNP (gene)	Melanoma			SCC			BCC		
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Ptrend	Cases (%)	Ptrend	Ptrend
rs2853676 (TERT)									
CC	470 (56.0)	99 (45.4)		154 (54.8)			156 (54.9)		
CT	316 (37.6)	97 (44.5)		102 (36.3)			109 (38.4)		
TT	54 (6.4)	22 (10.1)		25 (8.9)			19 (6.7)		
Additive OR ^a (95% CI)		1.43 (1.14–1.81)	0.002	1.09 (0.88–1.35)	0.43		1.04 (0.84–1.29)	0.73	
Additive OR ^b (95% CI)		1.45 (1.14–1.86)	0.003	1.07 (0.86–1.35)	0.53		1.05 (0.83–1.31)	0.71	
Additive OR ^c (95% CI)		1.43 (1.13–1.82)	0.003	1.09 (0.88–1.37)	0.43		1.03 (0.83–1.29)	0.79	
rs2242652 (TERT)									
GG	535 (71.2)	125 (62.2)		168 (66.7)			191 (71.0)		
GA	197 (26.2)	65 (32.3)		72 (28.6)			71 (26.4)		
AA	19 (2.5)	11 (5.5)		12 (4.76)			7 (2.6)		
Additive OR ^a (95% CI)		1.50 (1.14–1.98)	0.004	1.25 (0.96–1.62)	0.09		1.01 (0.77–1.33)	0.94	
Additive OR ^b (95% CI)		1.52 (1.13–2.04)	0.01	1.26 (0.96–1.66)	0.10		1.05 (0.79–1.39)	0.75	
Additive OR ^c (95% CI)		1.47 (1.10–1.96)	0.01	1.27 (0.97–1.66)	0.09		0.98 (0.74–1.30)	0.89	
rs2736100 (TERT)									
CC	217 (26.1)	64 (30.5)		95 (34.3)			90 (32.8)		
CA	399 (48.0)	91 (43.3)		125 (45.1)			116 (42.3)		
AA	215 (25.9)	55 (26.2)		57 (20.6)			68 (24.8)		
Additive OR ^a (95% CI)		0.91 (0.74–1.12)	0.37	0.78 (0.64–0.94)	0.01		0.85 (0.70–1.03)	0.09	
Additive OR ^b (95% CI)		0.95 (0.76–1.20)	0.68	0.79 (0.65–0.97)	0.02		0.85 (0.70–1.03)	0.10	
Additive OR ^c (95% CI)		0.91 (0.73–1.12)	0.37	0.80 (0.66–0.98)	0.03		0.84 (0.69–1.02)	0.07	
rs2075786 (TERT)									
GG	320 (40.6)	86 (41.7)		102 (38.3)			92 (34.8)		
GA	387 (49.0)	96 (46.6)		135 (50.8)			127 (48.1)		
AA	82 (10.4)	24 (11.7)		29 (10.9)			45 (17.0)		

SNP (gene)	Melanoma		SCC		BCC	
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)
rs2853676 (TERT)						
Additive OR ^a (95% CI)		1.02 (0.80–1.29)	0.90	1.07 (0.86–1.33)	0.54	1.32 (1.07–1.63)
Additive OR ^b (95% CI)		1.03 (0.80–1.33)	0.81	1.06 (0.85–1.33)	0.59	1.30 (1.05–1.62)
Additive OR ^c (95% CI)		1.03 (0.81–1.31)	0.84	1.07 (0.86–1.34)	0.53	1.34 (1.08–1.66)
rs401681* (TERT-CLPTMIL)						
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)
CC	268 (33.1)	53 (25.5)		81 (30.5)		112 (39.6)
CT	387 (47.8)	97 (46.6)		147 (55.3)		115 (40.6)
TT	154 (19.0)	58 (27.9)		38 (14.3)		56 (19.8)
Additive OR ^a (95% CI)		1.37 (1.10–1.69)	0.004	0.96 (0.78–1.17)	0.67	0.89 (0.74–1.08)
Additive OR ^b (95% CI)		1.37 (1.08–1.72)	0.01	0.90 (0.73–1.11)	0.33	0.89 (0.73–1.08)
Additive OR ^c (95% CI)		1.33 (1.07–1.66)	0.01	0.97 (0.79–1.19)	0.75	0.86 (0.71–1.04)
rs1772186 (TNKS2)						
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)
TT	544 (69.6)	160 (77.3)		190 (72.2)		183 (69.1)
TC	217 (27.7)	45 (21.7)		66 (25.1)		75 (28.3)
CC	21 (2.7)	2 (1.0)		7 (2.7)		7 (2.6)
Additive OR ^a (95% CI)		0.67 (0.48–0.93)	0.02	0.91 (0.69–1.20)	0.50	1.01 (0.78–1.32)
Additive OR ^b (95% CI)		0.64 (0.45–0.91)	0.01	0.93 (0.70–1.24)	0.64	1.02 (0.77–1.35)
Additive OR ^c (95% CI)		0.69 (0.50–0.97)	0.03	0.90 (0.68–1.19)	0.47	0.98 (0.75–1.28)
rs10509637 (TNKS2)						
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)
AA	589 (69.5)	161 (75.6)		203 (72.2)		203 (70.5)
AG	239 (28.2)	50 (23.5)		74 (26.3)		78 (27.1)
GG	19 (2.2)	2 (0.9)		4 (1.4)		7 (2.4)
Additive OR ^a (95% CI)		0.73 (0.53–1.00)	0.05	0.87 (0.67–1.15)	0.33	0.97 (0.75–1.26)
Additive OR ^b (95% CI)		0.70 (0.50–0.98)	0.04	0.89 (0.67–1.18)	0.43	0.96 (0.73–1.27)
Additive OR ^c (95% CI)		0.74 (0.54–1.02)	0.07	0.86 (0.65–1.14)	0.29	0.94 (0.72–1.22)
rs2981096 (TRF1)						
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)

SNP (gene)	Melanoma			SCC			BCC		
	Controls (%)	Cases (%)	Ptrend	Cases (%)	Ptrend	Cases (%)	Cases (%)	Ptrend	Ptrend
rs2853676 (TERT)									
AA	790 (92.3)	187 (85.8)		258 (91.2)		269 (92.4)			
AG	64 (7.5)	31 (14.2)		25 (8.8)		21 (7.2)			
GG	2 (0.2)	0 (0.0)		0 (0.0)		1 (0.3)			
Additive OR ^a (95% CI)		1.87 (1.19–2.91)	0.006	1.12 (0.70–1.79)	0.63	1.01 (0.62–1.62)		0.98	
Additive OR ^b (95% CI)		2.02 (1.25–3.24)	0.004	1.01 (0.62–1.64)	0.98	0.99 (0.60–1.62)		0.96	
Additive OR ^c (95% CI)		1.97 (1.24–3.11)	0.004	1.16 (0.72–1.86)	0.56	1.04 (0.65–1.69)		0.86	
rs8061382 (TRF2)									
TT	753 (94.6)	188 (90.8)		252 (95.1)		238 (91.2)			
TA	43 (5.4)	19 (9.2)		13 (4.9)		22 (8.4)			
AA	0 (0.0)	0 (0.0)		0 (0.0)		1 (0.4)			
Additive OR ^a (95% CI)		1.81 (1.03–3.19)	0.04	0.88 (0.47–1.67)	0.70	1.75 (1.05–2.93)		0.03	
Additive OR ^b (95% CI)		1.76 (0.95–3.27)	0.07	1.02 (0.52–2.00)	0.96	1.90 (1.09–3.32)		0.02	
Additive OR ^c (95% CI)		1.76 (0.98–3.16)	0.06	0.94 (0.50–1.79)	0.85	1.67 (0.98–2.86)		0.06	
rs3785074 (TRF2)									
TT	440 (52.8)	102 (48.6)		144 (53.1)		121 (43.5)			
TA	336 (40.3)	95 (45.2)		111 (41.0)		138 (49.6)			
AA	57 (6.8)	13 (6.2)		16 (5.9)		19 (6.8)			
Additive OR ^a (95% CI)		1.10 (0.86–1.41)	0.44	0.97 (0.77–1.21)	0.77	1.27 (1.02–1.58)		0.03	
Additive OR ^b (95% CI)		1.05 (0.81–1.36)	0.74	0.97 (0.76–1.22)	0.77	1.26 (1.00–1.58)		0.05	
Additive OR ^c (95% CI)		1.07 (0.83–1.37)	0.62	0.97 (0.77–1.22)	0.77	1.29 (1.03–1.61)		0.03	

Additive OR^a was calculated based on the unconditional logistic regression adjusted for age.

Additive OR^b was calculated based on the unconditional logistic regression adjusted for age, constitutional susceptibility score (tertiles), family history of skin cancer (yes/no), the number of lifetime severe sunburns that blistered (none, 1–5, 6–11, >11), sunlamp use or tanning salon attendance (yes/no), cumulative sun exposure while wearing a bathing suit (tertiles), and geographic region.

Additive OR^c was calculated based on the unconditional logistic regression adjusted for age and telomere length.

*For rs401681, we used “TT” genotype as the reference to be consistent with previous GWAS (Rafnar et al. 2009).

*Additive OR^a (95% CI) of the rs401681[C] was 0.73 (0.59–0.91) for melanoma risk.

*Additive OR^b (95% CI) for the rs401681[C] was 0.73 (0.58–0.93) for melanoma risk.

*Additive OR^c (95% CI) for the rs401681[C] was 0.75 (0.60–0.93) for melanoma risk.