A melanoma risk score in a Brazilian population *

Um escore de risco para melanoma em uma população brasileira

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Abstract: BACKGROUND: Important risk factors for cutaneous melanoma (CM) are recognized, but standardized scores for individual assessment must still be developed.
OBJECTIVES: The objective of this study was to develop a risk score of CM for a Brazilian sample.
METHODS: To verify the estimates of the main risk factors for melanoma, derived from a meta-analysis (Italian-based study), and externally validate them in a population in southern Brazil by means of a case-control study. A total of 117 individuals were evaluated. Different models were constructed combining the summary coefficients of different risk factors, derived from the meta-analysis, multiplied by the corresponding category of each variable for each participant according to a mathematical expression.
RESULTS: the variable that best predicted the risk of CM in the studied population was hair color (AUC: 0.71; 95% CI: 0.62-0.79). Other important factors were freckles, sunburn episodes, and skin and eye color. Consideration of other variables such as common nevi, elastosis, family history, and premalignant lesions did not improve the predictive ability of the models.
CONCLUSION: The discriminating capacity of the proposed model proved to be superior or comparable to that of previous risk models proposed for CM.
Keywords: Melanoma; Nevi and melanomas; Risk; Risk factors

Resumo: FUNDAMENTOS: importantes fatores de risco para melanoma cutâneo são reconhecidos, mas escores padronizados para avaliação individual ainda precisam ser elaborados.
OBJETIVOS: o objetivo deste estudo foi desenvolver um escore de risco de melanoma cutâneo para uma amostra brasileira.
MÉTODOS: verificar as estimativas dos principais fatores de risco para melanoma, derivado de uma meta-análise (estudo de base italiano) e, externamente, validar em uma população do sul do Brasil por um estudo caso-controle. Um total de 117 indivíduos foram avaliados.
RESULTADOS: a variável com maior poder preditivo para o risco de melanoma cutâneo na população estudada foi a cor do cabelo (AUC: 0,71, IC 95%: 0,62-0,79). Outros fatores importantes para o modelo foram: sardas, queimaduras solares, e cor de pele e cor dos olhos. Adicionando outras variáveis, como os nevos comuns, elastose, história familiar e lesões pré-malignas não houve melhora da capacidade preditiva.
CONCLUSÃO: A capacidade discriminatória do modelo proposto mostrou-se superior ou comparável aos modelos de risco anteriores propostos para melanoma cutâneo.
Palavras-chave: Fatores de risco; Melanoma; Nevos e melanomas; Risco

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INTRODUCTION

The incidence of cutaneous melanoma (CM) has increased over the last decades among Caucasians. CM is, in fact, the malignancy with the highest increase rates among this population, with the exception of lung cancer in women.[1,2] In 2012 in Brazil, 3,170 new cases of CM were estimated for men, and 3,060 new cases for women, a total of 6,230 new cases. The highest estimated incidence rates of CM are in the Southern Region of the country (5.67/100,000 inhabitants for males and 5.60/100,000 for females).[3]

Although the incidence of CM is increasing, the disease remains a relatively rare malignancy.[4] Therefore, prevention campaigns targeting the general population may have little benefit. However, concern with primary and secondary prevention is important, since CM is a disease with high mortality rates, and early detection may change its outcome. The prognosis of this type of cancer may be good when it is detected in its early stages. Over the last years, patients with CM have shown better survival rates, mostly due to early diagnosis.[4-9] In developed countries, the mean estimated 5-year survival rate is 73%, while in developing countries it is 56%. The estimated mean world rate is 69%.[3]

Some risk factors for CM are well recognized. They are family history of melanoma (first degree relatives), dysplastic nevus syndrome, eye and hair color, skin color, phototype and tanning capacity, presence of freckles and/or pre-cancerous lesions (actinic keratoses), large number of common acquired nevi, presence of atypical nevi, and sun exposure and other environmental factors.[10-17] Although sun exposure is considered the main environmental risk factor for CM, the relation between sun exposure and melanoma is complex.[18] Some CMs seem to be strongly associated with sunlight and, potentially, sunlamps and tanning beds.[14] Sunburn episodes in childhood are most strongly associated with CM.[12] Other potential risk factors are diet and occupation, as well as environmental pollution and pesticides.[13,15,16,17] However, these last two have not yet been extensively studied.

Considering constitutional risk factors, it has been reported that individuals with light-brown, blonde or red hair present at least a two-fold risk of developing CM when compared to individuals with dark-brown or black hair.[19-24] Individuals with blue, gray or green eyes also show a high risk of developing CM. However, this association is not as strong as that with hair color.[19,20,23] Fair skin, lack of tanning capacity (phototypes I and II), and presence of multiple freckles (especially in adults) have also been considered factors associated with an increased risk for CM.[19,21,23,25-27] The most important factor associated with the development of melanomas in individuals with fair skin may be related to their incapacity to protect against the damage caused by UV radiation because they have less melanin, which is effective against the harmful effects of oxygen radicals generated by the sun.[28] UVB susceptibility is significantly higher in individuals with a family history of skin cancer and those of Northern European ancestry.[29]

In addition to phenotypic traits, it has been suggested that the presence of large numbers of common acquired nevi and the presence of atypical nevi identify subjects at a higher risk for CM. It has been shown that adults with 25 common acquired nevi or more (>=2 mm) are twice as likely to develop melanoma than subjects with fewer than 25 nevi. People with one or more dysplastic nevi (<=5 mm) are twice as likely to develop the disease than people with none.[20,30,31] Nevi on unusual sites (dorsum of the feet, buttocks and anterior scalp) are risk factors of melanoma and remained significant after adjustment for atypical nevi.[20,31] Family history of melanoma and dysplastic nevi also appear as risk factors of CM.[32]

The role of sunscreens has not been clearly defined yet. According to the same authors, their use is associated with a two-fold increase in the risk of CM.[21,22,23,33] This may be explained by the fact that individuals extend their sun exposure and/or substitute protective clothing with sunscreens. A recent study suggests that sunscreen use leads to longer sun exposure when it is intentional, but not when it is unintentional.[34]

In contrast to previous studies, the publication of a randomized clinical trial by Green et al conducted in Australia between 1996-2006. showed that CM can be prevented with the regular use of an SPF 16 sunscreen.[35]

Although several studies have examined numerous potential risk factors for CM, few studies have investigated the relationship between these factors and individual melanoma risk.[36,37]

The great variability in CM incidence seen in different countries suggests that a large sample size is required for developing a model in which the predictive ability is stable across countries. Therefore, meta-analysis studies, which combine risk estimates from many studies and appreciate differences due to genetic, geographic and climatic conditions, allow the development of a risk score to identify subjects at a high risk of CM.[10-12]

The aim of this study was to develop a melanoma risk score using the estimates of the main risk factors for melanoma, which were derived from a meta-analysis, and externally validate it in a Brazilian population.

METHODS

This study was part of an Italian project for the primary and secondary prevention of CM coordinated by Istituto dell'Immacolata (IDI-IRCCS) of Rome, Italy. Since a large sample is required to develop a risk model in which the predictive ability is stable, the results of three meta-analyses, which combined risk estimates from many studies, were used to develop a risk score for CM. A systematic meta-analysis of observational studies of CM (comprising 110 independent published studies, from 1966 to 2002, of pigmented lesions, and from 1984 to 1999 of other risk factors) was carried out at IDI-IRCCS to identify the main risk factors for CM.[10-12] Summary coefficients of the major risk factors were derived from the meta-analysis (Table 1). The main risk factors for CM studied by means of meta-analysis were exposure to ultraviolet radiation, sunburn episodes, actinic damage, family history of melanoma, phenotype characteristics, pigmented lesions, and skin phototype. All these risk factors were considered for the construction of the risk model for CM.

The predictive ability of the various models was tested in a case-control study using blinded data (the status case/control of subjects was unknown). This case-control study of CM was conducted at the Department of Dermatology of the University Hospital of the Federal University of Rio Grande do Sul (Hospital de Clinicas de Porto Alegre) and in the dermatological outpatient clinic of the Secretary of Health of Rio Grande do Sul, Brazil. Cases and controls were residents in the urban area of Porto Alegre and enrolled between 2005 and 2008. The ethical committee of Hospital de Clinicas de Porto Alegre approved the study, and a written consent was obtained from all participants. A total of 119 subjects (53 cases and 66 controls) were invited to participate and 117 gave their written consent. Cases were individuals with a new histologically-confirmed diagnosis of primary malignant CM.

Controls were selected from patients in the same hospital during the same study period. They were from the General Surgery, Vascular Surgery, Orthopedics, Otorhinolaryngology, and General Medicine wards. Controls were from the same geographical area and did not have a personal history of skin cancer. Controls were matched to cases by sex and age.

After signing a written consent, patients and controls orally answered an extensive and detailed questionnaire that covered family history, life habits (dietary habits, leisure time), occupation, use of drugs, oral contraceptives and hormones, smoking, sunlight and UV lamp exposure, use of sunscreens, contact with radiation, pesticides (agricultural and domestic), and other factors that could be related to CM. Age, gender, skin, hair and eye color, and phototype were also registered.

After answering the questionnaire, patients were submitted to a full-body skin examination, except for the scalp and genitalia, in order to detect and count congenital, acquired and dysplastic nevi, freckles, and signs of photodamage.[37]

Statistical Analysis

Different models were constructed combining the summary coefficients of different risk factors (β_i), derived from the meta-analysis, and multiplied by the corresponding category of each variable for each participant (X_i) according to the following mathematical expression: $e^{\beta i+Xi+\beta 2+x2+..\beta\alpha+X\alpha}$. For instance, a subject with blonde hair, light eyes and fair skin, with freckles and reported sunburn episodes, will have a score of 26 $=e^{0.50+0.48+0.72+0.84+0.73}$; a subject with dark brown hair and eyes, fair skin, no freckles and no reported sunburn episodes will have a score of 2 $=e^{0.72}$. A practical predictor of subjects at high risk of developing CM was devised and can be provided for use in clinical practice.

Factors from the physical examination considered for model construction, were skin, eye and hair color, presence of freckles, presence of elastosis and atypical nevi, and the number of nevi, whereas factors from the questionnaire were family history of CM, sun exposure, and sunburn episodes throughout life. Pooled risk estimates and coefficients derived from the meta-analysis are summarized in table 1.

To select variables for inclusion in our risk model, we assessed a variety of factors. The variables included in the models were categorized as following: number of common nevi over the entire body (6 categories); presence of freckles in childhood (yes/no); skin color (2 categories); eye color (2 categories); hair color (4 categories); skin phototype (4 categories), presence of elastosis (yes/no), number of atypical nevi, family history of CM (yes/no); sunburn epidoses in childhood (yes/no); sunburn episodes in adulthood (yes/no); sunburn episodes throughout life (yes/no) and total sun exposure (2 categories). Regression models were constructed using the 14 variables; the Receiver Operating Characteristic (ROC) curve in this study was used to assess the predictive ability of each risk model. Regression models are often evaluated by establishing a cut-off point (e.g. AUC=0.51); predictive probabilities below the cut-off point are treated as predictors of no event, and probabilities at or above the cut-off point are considered to be predictors of the event. A forward approach was used for fitting variables in the models starting from a single variable. We started the models with hair color (AUC: 0.71; 95%CI: 0.62-0.79) because it was the highest AUC among the one-variable models. Next, we compared the predictive ability (area under the ROC curves) of hair color alone with that of other models

TABLE 1: Summary coefficients of the risk factors from the Meta-Analysis

	RR exp(ß)	La(RR) ß
Hair colour[3]		
black/ darck brown	1	...
light brown	1.34	0.29257
fair/ blond	1.65	0.50078
red	2.86	1.05082
Eyes colour[3]		
black/ dark and light brown	1	...
blue/ grey/ green	1.62	0.48039
Skin colour[3]		
dark	1	…
fair	2.06	0.72271
Skin phototype (Fitzpatrick)*[3]		
IV	1	…
III	1.77	0.57098
II	1.84	0.60977
I	2.09	0.73716
Presence of freckles[3]		
no	1	…
yes	2.32	0.84166
Family history of melanoma[3]		
no	1	…
yes	1.74	0.55389
Numbers of common naevi[1]		
[0-15]	1	…
[16-40]	1.47	0.38513
[41-60]	2.24	0.80648
[61-80]	3.26	1.18173
[81-100]	4.74	1.55604
≥101	6.89	1.93007
Presence of elastosis[3]		
no	1	…
yes	2.02	0.70310
Presence of actinic damage†[3]		
no	1	…
yes	4.28	1.45395
Sunburns episodes in childhood[2]		
no	1	…
yes	2.24	0.80648
Sunburns episodes in adulthood[2]		
no	1	…
yes	1.92	0.65233
Sunburns episodes in all life[2]		
no	1	…
yes	2.08	0.73237
Total exposure[2]		
low	1	…
high	1.34	0.29267

1 Gandini S et al. Meta-analysis of risk factors for cutaneous melanoma: **I.** Common and atypical naevi. Eur J Cancer. 2005; 41: 28-44.
2 Gandini S et al. Meta-analysis of risk factors for cutaneous melanoma: **II.** Sun exposure. Eur J Cancer. 2005;41:45-60.
3 Gandini S et al. Meta-analysis of risk factors for cutaneous melanoma: **III.** Family history, actinic damage and phenotypic factors. Eur J Cancer. 2005;41:2040-2059.
* **I:** always burns and never tans; **II:** often burns and tans minimally; **III:** rarely burns **†** cutaneous epithelioma and/or actinic keratosis.

with more variables. The variables that did not contribute to a better fitting of the models were excluded. A total of 105 models were built and tested. The best fitting model included five variables (model A). They were hair color, skin color, eye color, sunburn episodes throughout life, and the presence of freckles. To test the difference in AUC of different models, we used the test for equality, a non-parametric method based on Mann-Whitney U-statistics which takes into consideration the correlated nature of the data.[38,39]

All analyses were done using the statistical software package PC-STATA (Stata 9.0; StataCorp LP, College Station, Texas 77845 USA).

RESULTS

The mean age of the study population was 57 years (56.4% female; 43.6% male). Phototype II (44.4%), dark eyes (56.4%) and dark hair (50.4%) were most frequently observed; most patients did not have freckles (69.0%) or atypical nevi (88.9%); 48.7% presented less than 15 common melanocytic nevi. Table 2 shows the characteristics of the population used for construction of the risk models.

Using the-step-forward technique to construct the models, we observed that the variable that best predicted the risk of CM in the studied population was hair color (AUC: 0.71; 95%CI: 0.62-0.79). We observed that by adding freckles to the first model (hair color alone) the predictive value of the model increased to 78% (AUC: 0.78; 95%CI: 95%CI: 0.69-0.85). After including sunburn episodes, the predictive value increased to 82% (AUC: 0.82; 95%CI: 95%CI: 0.73-0.89). After including skin and eye color to the later model, the predictive ability increased to 85% (model A, Table 3). Adding other variables such as common nevi, elastosis, family history and premalignant lesions did not improve the predictive ability of the models (Table 3). No statistical difference was found between model A, which included five-variables, and the other risk models with six-variables, except for model E (model A plus elastosis), which was inferior to model A (P=0.001) (Table 3).

The candidate AUC (the one with the highest predictive ability) was 0.85 (95%CI: 0.77-0.91) (Table 3). Sensitivity and specificity were calculated for various cut-off points. The optimal cut-off point with comparable specificity was 3 and more. At the cut-off point of three and more, sensitivity and specificity were 81% and 67%, respectively. The median risk scores for cases and controls in the study were 9.3 and 2.1, respectively.

Table 4 shows the characteristics of the study population classified as "high risk" by the best model. Subjects considered at "high risk" for CM tended to have light hair and fair skin, freckles in childhood,

TABLE 2: Characteristics of the Brazilian Study by status

	Total(N=117) No.*(%)	cases (N=64) N.*(%)	controls(N=53) N.*(%)
Hair colour			
black/dark brown	59(50.4)	22(34.4)	37(69.8)
light brown	33(28.2)	20(31.3)	13(24.5)
fair/blond	21(17.9)	18(28.1)	3(5.7)
red	4(3.4)	4(6.2)	0(0)
Eye colour			
black/dark and light brown	66(56.4)	26(40.6)	40(75.5)
blue/grey/green	51(43.6)	38(59.4)	13(24.5)
Skin colour			
dark	54(46.2)	18(28.1)	36(67.9)
fair	63(53.8)	46(71.9)	17(32.1)
Skin phototype§			
IV	3(2.6)	2(3.1)	1(1.9)
III	21(17.9)	11(17.2)	10(18.9)
II	52(44.4)	32(50)	20(37.7)
I	41(35.0)	19(29.7)	22(41.5)
Presence of freckles			
no	78(69.0)	31(51.7)	47(88.7)
yes	35(31.0)	29(48.3)	6(11.3)
Family history of skin cancer			
no	117(100)	64(100)	53(100)
yes	0	0	0
Common nevi (n)			
[0-15]	57(48.7)	34(53.1)	23(43.4)
[16-40]	28(23.9)	12(18.8)	16(30.2)
[41-60]	17(14.5)	10(15.6)	7(13.2)
[61-80]	8(6.8)	3(4.7)	5(9.4)
[81-100]	3(2.6)	1(1.5)	2(3.8)
≥101	4(3.4)	4(6.3)	0(0)
Atypical nevi (n)			
0	104(88.9)	55(85.9)	49(92.5)
≥1	13(11.1)	9(14.1)	4(7.5)
Presence of elastosis			
no	66(57.9)	40(64.5)	26(50.0)
yes	48(42.1)	22(35.5)	26(50.0)
Presence of actinic damage†			
no	87(74.4)	39(60.9)	48(90.6)
yes	30(25.6)	25(39.1)	5(9.4)
Sunburns episodes in childhood			
no	68(64.2)	31(55.4)	37(74)
yes	38(35.8)	25(44.6)	13(26)
Sunburns episodes in adulthood			
no	56(47.9)	23(35.9)	33(62.3)
yes	61(52.1)	41(64.1)	20(37.7)
Sunburns episodes in all life			
no	35(31.0)	10(16.1)	25(49)
yes	78(69.0)	52(83.9)	26(51)
Total exposure			
low	87(76.3)	44(69.8)	43(84.3)
high	27(23.7)	19(30.2)	8(15.7)

* totals may vary because of missing value.

† cutaneous epithelioma and/or actinic keratosis.
§ I: always burns, never tans; II: often burns, tans minimally; III: rarely burns, tans well; IV: never burns, tans profusely.

TABLE 3: Description of some risk models in the Brazilian population and the Area Under Curve (AUC)

Model	Variables	AUC(95%CI)	P-Value*
(referent) A	hair colour presence of freckles sunburns in all life skin colour eye colour	0.85(0.77-0.91)	…
B	A + common nevi in the whole body	0.84(0.76-0.91)	0.77
C	A + atypical nevi	0.86(0.77-0.91)	0.48
D	A + pre-malignant lesions	0.85(0.77-0.91)	0.99
E	A + elastosis	0.80(0.73-0.88)	0.004

* P-value for test equality of ROC area of each model against model A (referent)

presence of premalignant skin lesions, and sunburn episodes in childhood.

DISCUSSION

Melanoma has many features that make it a good target for early detection. It has become increasingly common and can be cured in its early stages with simple inexpensive surgery. Routine screening of the general population for CM using complete skin exams is theoretically possible, but it would be very costly because of the large number of examinations required. Moreover, it would be inefficient because of the many examinations with negative results. Targeting high-risk subjects would improve efficiency and help select the appropriate individuals for interventions. Interventions in high-risk individuals may lead to the detection of early-stage curable disease or to a decrease in the risk of developing CM.

Our five-variable model had a discriminatory ability of 85% of CM cases. Four individual risk factors (skin color; hair and eye color, and freckles) and reported sunburn episodes in childhood were the variables included in the model because they required the provider to have specialized diagnostic skills, to ask detailed questions or conduct more extensive patient examinations. Model A was chosen as the candidate model because it included variables that were simple and quickly, easily and accurately identified during routine healthcare evaluations and had a good discriminatory ability. Model B, which was as good as model A, included number of nevi.

In very high-risk individuals (e.g. members of hereditary melanoma kindreds with dysplastic nevi) screening and interventions have resulted in earlier diagnosis and reduced mortality.[40-42] However, familial melanoma only represents 10% of all melanomas.[40-42] Therefore, there is still much to be done regarding sporadic CM prevention. Routine screening for CM has considerable implications in terms of health care costs and unwanted effects on people. However, if

TABLE 4: Characteristics of the Brazilian subjects according to the cut-off ≥ 3 or tbe candidate model

	"AI risk" (N=65) No* (%)	"Not at risk (N=45) No* (%)
Status		
cases	48(81.4)	11(18.6)
controls	17(33.3)	34(66.7)
Sex		
males	26(53.1)	23(46.9)
females	39(63.9)	22(36.1)
Age (yr)		
< 25	2(50.0)	2(50.0)
25-34	5(55.6)	4(44.4)
35-44	4(28.6)	10(71.4)
45 54	8(53.3)	7(46.7)
55-64	11(36.7)	19(63.3)
65-74	8(29.6)	19(70.4)
≥75	7(63.6)	4(36.4)
Hair colour†		
black/dark brown	21(38.2)	34(61.8)
light brown	21(67.7)	10(32.3)
fair/blond	19(95.0)	1(5.0)
red	4(100)	0
Eye colour†		
black/dark and light brown	22(34.9)	41(65.1)
blue/grey/geen	43(91.5)	4(8.5)
Skin colour†		
dark	10(19.2)	42(80.5)
fair	55(94.8)	3(5.2)
Skio phototype§		
IV	0	3(100)
III	5(25.0)	15(75.0)
II	28(57.1)	21(42.9)
I	32(84.2)	6(15.8)
Presence of freckles		
no	33(43.4)	43 (56.6)
yes	32(94.1)	2(5.9)
Family history of skin cancer		
no	65(59.1)	45(40.9)
yes	0	0
Common nevi (n)		
[0-15]	37(68.5)	17(31.5)
[16-40]	13(48.1)	14(51.9)
[41-60]	9(56.3)	7(43.7)
[61-80]	2(33.3)	4(66.7)
[81-100]	1(33.3)	2(66.7)
≥101	3(75.0)	1(25.0)
Atypical nevi (n)		
0	57(58.2)	41(41.8)
≥1	8(66.7)	4(33.3)
Presence of elastosis		
no	37(59.7)	25(40.3)
yes	25(55.6)	20(44.4)
Presence of actinic damage		
no	41(50.0)	41(50.0)
yes	24(85.7)	4(14.3)
Sunburns episodes in childhood		
no	33(50.0)	33(50.0)
yes	28(73.7)	10(26.3)
Sunburns episodes in adulthood		
no	24(47.1))	27(52.9)
yes	41(68.5)	18(30.5)
Sunburns episodes in all life†		
no	10(29.4)	24(70.6)
yes	55(72.4)	21(27.6)
Total uposure		
low	48(58.5)	34(41.5)
high	16(64.0)	9(36.0)

* totals may vary because of missing value.
† risk factors involved in risk model A
§ I: always burns, never tans; II: often burns, tans minimally; III: rarely burns, tans well; IV: never burns, tans profusely.

individuals at high risk could be identified, surveillance could target only this group. These interventions could include complete skin examination, counseling and education to avoid sun exposure, regular self-examination, and professional surveillance.

The discriminatory ability of our model was higher than that of previously proposed risk models for CM (0.62) and comparable to the melanoma risk model proposed by Fears et al. (0.70-0.80) and to other risk models for other cancer sites (0.57-0.72).[36,37,43-45]

Although the absence of several known CM risk factors may be seen as a potential limitation of our model, this is likely of little impact, as many of the excluded factors are highly correlated with those included in the model. Another limitation of the model is that it was validated in a retrospective study, and the best design to answer prognostic questions is a cohort study. However, prognostic models obtained from only one cohort study may have restricted generalizability.[46] It has been suggested that for prediction models that need a long follow-up for gathering of enough outcome events (e.g. melanoma) retrospective data can be used.[47] Another limitation of the model is that it was validated in a small case-control study. Nonetheless, it has been suggested that, for each candidate predictor studied, 10 events are required.[47] We believe that the potential usefulness of the model will encourage its testing by other investigators in larger samples in Brazil.

The model has a number of strengths. As a predictive model with potential value in general practice, it uses readily obtainable variables. It is flexible and can be easily used in general practice for counseling and education to avoid sun exposure and to encourage regular self-examination and professional surveillance. Interventions in high-risk individuals may lead to the detection of early-stage curable disease or decrease the risk of developing CM.

CONCLUSION

Our study suggests that subjects at high risk for developing CM could be identified with an inexpensive and simple tool that can be used by primary healthcare providers with minimal training, especially in countries not yet prepared to face the higher frequency of CM. ❑

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