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ORIGINAL ARTICLE

Differences in individual and environmental factors between cutaneous melanoma and atypical Spitz tumour in children and adolescents

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Abstract

It is not known if children and adolescents with atypical Spitz tumour and cutaneous melanoma differ in terms of etiological factors. The aim of this study was to explain differences in individual and environmental factors between cutaneous melanoma and atypical Spitz tumour. In the context of a study on melanocytic lesions, all subjects aged under 20 years with either cutaneous melanoma or atypical Spitz tumour were included ($N = 105$). Information on socio-demographic characteristics, individual and environmental factors were collected for both mother and child. The Fisher's exact test and the Mann–Whitney U test were used for categorical variables and continuous variables respectively. A multivariate logistic model was used to explain differences in outcome by differences in explanatory variables. In comparison to patients with cutaneous melanoma, patients with atypical Spitz tumour had less freckles ($p = 0.020$), lower number of common nevi ($p = 0.002$), and lower body mass index ($p = 0.001$) and experienced less sunburns episodes ($p = 0.008$). However, in the multivariate analysis, only a low number of common nevi remained statistically significant. Children and adolescents with cutaneous melanoma have a high number of nevi in comparison to the same-age group with atypical Spitz tumour.

Conclusion: The results of this study suggest that the only difference in individual and environmental risk factors between cutaneous melanoma and atypical Spitz tumour in children and adolescents is the number of nevi.

What is Known:

- *Atypical Spitz tumours and cutaneous melanoma in children and adolescents are clinically similar, but compared with melanoma, they have a good overall prognosis.*
- *Risk factors for cutaneous melanoma in children and adolescents are similar to the ones found in adults in the literature*

What is New:

- *Differences in individual and environmental risk factors for atypical Spitz tumour in children and adolescents are described for the first time in this study.*
- *Individual and environmental factors for atypical Spitz tumour in children and adolescents are comparable to cutaneous melanoma, except for the presence of low number of nevi.*

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Abbreviations

BMI	Body mass index
CI	Confidence intervals
IARC	International Agency for Research on Cancer
OR	Odds ratio
SD	Standard deviation

Introduction

Although cutaneous melanoma in young people (< 20 years old) is rare, since it represents less than 1% of all melanoma cases, it is the most common skin cancer in that age group [1, 2]. Incidence rises with increasing age, and it is higher in females than in males [3]. Moreover, melanoma in children displays unique characteristics, given that children with melanoma have a higher rates of lymph node metastases in comparison to adults with similar tumour characteristics [4].

Epidemiological studies conducted in the USA and in Europe show that incidence of melanoma in children and adolescents varies from 0.7 to 0.8 cases per million in the first decade to 10 cases per million in the second decade [5]. However, the true incidence is difficult to determine due to inclusion of atypical Spitz tumour, which leads to overdiagnosis [2, 6].

Most of the atypical Spitz tumours occur in subjects aged less than 30 years [3]. Atypical Spitz tumours are lesions with intermediate architecture and cytomorphology between Spitz nevus and melanoma. The clinical appearance of an atypical Spitz tumour may be similar to paediatric melanoma (e.g. amelanotic, bleeding/bump, colour uniformity). However, by comparison to melanoma, they have a good overall prognosis, despite the common involvement of the sentinel lymph node [6–8].

It has been suggested that risk factors for cutaneous melanoma in young subjects, in particular adolescents, are similar to the ones seen in adults and they include family history of melanoma, skin colour, early sun exposure and indoor tanning beds exposure [9, 10]. Moreover, in adults, ionizing radiation and pesticide exposure have been associated with an increased risk of cutaneous melanoma [11, 12]. Interestingly, there is evidence that exposure to pesticides [13] and ionizing radiation [14] during pregnancy may also lead to childhood cancer.

It is not known whether children with atypical Spitz tumour differ from children with cutaneous melanoma in terms of risk factors. Therefore, the aim of this study was to explore any differences in individual and environmental risk factors between atypical Spitz tumours and cutaneous melanoma in persons less than 20 years.

Methods

We conducted this study between years 2015 and 2020, and we included all patients aged < 20 years with histologically confirmed diagnosis of either atypical Spitz tumour or cutaneous melanoma ($N = 105$). The study was performed in the reference hospital for skin diseases (IDI-IRCCS) in Rome, Italy, and it was approved by the IDI-IRCCS ethical committee (no. 425 CE/2014). Patient informed consent and parental informed consent in patients aged < 14 years were obtained. Participants were invited for the interview and clinical examination of pigmented lesions by dermatologists. Questionnaires were administrated by trained dermatologists.

Data on sociodemographic characteristics, personal medical history of the patient (including family history of skin cancer), phenotypic traits (skin type, skin, hair and eye colour), height and weight, physical activity, sunburn history, lifetime sunlight exposure, sun bed and/or lamp exposure and diet was obtained using a structured validated questionnaire used in other epidemiological studies [12, 15, 16]. Another structured questionnaire addressed to the patient's mother to collect information on socio-demographic characteristics, occupation, use of medicines during pregnancy and radiation and pesticide exposure before and during pregnancy was used in the study. Information on smoking status of the mother was collected. Smokers were considered subjects that smoked at least one cigarette daily in the previous 6 months [17]. If the mother was considered a smoker according to the latter definition, we asked if she had smoked during pregnancy (yes/no).

Skin photo-type (burning and tanning tendency) was classified in the following categories III, IV and I, II [18]. Hair colour was classified as red, blonde and fair; light brown; dark brown; and black. Eye colour was divided into three categories: dark brown and black; light brown; and blue, grey and green. The pigmented lesions were identified and recorded according to the IARC protocol [19]. The number of nevi over the entire skin surface (except for the scalp, pubic region and perineum) was recorded and then classified as few (0–24) or many (≥ 25) [20].

The presence of freckles was classified in two categories (no/yes). Chronic sun exposure history was based on time spent outdoors during weekdays and weekends, estimated as average daily hours outdoors. On the basis of daily hours, cumulative number of hours spent outdoors during the week was calculated and classified in three categories (≤ 20; 21–34; ≥ 35 h weekly).

Information on sunburn episodes (sunburns causing pain and erythema and/or blisters for more than 24 h) and

sun protection behaviour (frequency of use of sunscreens (SPF ≥ 15) and the use of hats and/or T-shirt) was collected. Sunburn episodes was classified in three groups (no; yes, 1 episode; yes, ≥ 2 episodes). The frequency of use of sunscreens and hats and/or T-shirt was also categorized into two groups never/rarely and often/ever. Physical activity was assessed by asking how many times the subjects practiced sports weekly (no; yes, ≤ 2 times/week; yes, ≥ 3 times/week). To assess dietary habits, patients were requested to complete a food frequency questionnaire [16]. The frequency intake of all food groups was defined on a seven-point scale as the following: (i) never, (ii) less than monthly, (iii) less than weekly, (iv) one to two times per week, (v) three to four times per week, (vi) five to seven times per week and (vii) daily. Food items were subdivided into related groups and subgroups based on the type of phytochemical content such as tomatoes for lycopene; dark leafy green vegetables (spinach, chicory, beet leaves) for phenols, lutein and zeaxanthin; cruciferous vegetables (broccoli, cauliflower, cabbage) for phenols, isothiocyanates and indoles; and citrus fruit (oranges, tangerines) for b-cryptoxanthin. For each individual food or food group, the seven-point categorical scale was combined to form three categories representing low, medium and high consumption. Combination of categories was based on the overall distribution. Therefore, for some items such as fish consumption, only two categories were used.

The body mass index (BMI) was calculated by dividing the weight (kg) by the square of height (m), and World Health Organization growth reference values for children and adolescents were used [21]. Three BMI classes were created (< 18.5; 18.5–24.9; ≥ 25.0).

A validated 35-item structured questionnaire [12, 22] was used to assess residential pesticide exposure. The questionnaire included information on lifetime frequency and length of use of pesticides at domestic level indoors (pesticides used against mosquitoes, ants, flies, spiders, cockroaches, mice, wasps, moths, termites, mites) and outdoors (pesticides used in the terrace, yard, garden), the use of anti-pediculosis products and the use of repellents during the summer season.

Statistical analysis

Descriptive statistics, with frequencies and percentages, mean values and standard deviation (SD), were presented to describe demographic and clinical characteristics of the participants included in the study. To assess differences between atypical Spitz tumour and melanoma cases, the Fisher's exact test was used for categorical variables while the Mann–Whitney U test was used for continuous variables. The Shapiro–Wilk test was used to test for normality. Diagnosis was used as the dependent variable (0 = melanoma; 1 = atypical Spitz tumour). The unconditional logistic regression model was the method chosen for the univariate and multivariate statistical analysis. Using males and the low category groups as the reference point, the odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the other categories. All variables in the logistic regression models were entered as categorical variables. The likelihood test was used to decide whether to keep or eliminate each explanatory variable. Variables that were included in the multivariate models were sex, age, BMI, presence of freckles, common nevi and history of sunburns. Statistical analyses were performed using the statistical software STATA, release 15 (College Station, TX: StataCorp LCC).

Results

A total of 105 subjects were approached (76 cutaneous melanoma cases and 29 atypical Spitz tumour) and provided a written consent and were interviewed and had a full skin examination. The response was 70.5%. Among these, a total of 51 subjects had cutaneous melanoma (47.1% females; 52.9% males) and 23 subjects had atypical Spitz tumour (47.8% males; 52.2% females).

The mean ages of the cutaneous melanoma cases and atypical Spitz tumour were 15.2 years (SD 4.2) and 11.7 years (SD 4.8) respectively. In the group of atypical Spitz tumour, 9 subjects were aged less than 10 years (39.1%); in the group of cutaneous melanomas, only 4 subjects (7.8%). In our patients, the superficial spreading cutaneous melanoma was the most frequently seen histological type of melanoma (76.1%) and the trunk was the most common site (39.2%). The mean Breslow thickness was 1.10 (SD 1.01), 8.2% were ulcerated, 14.3% had a high mitotic rate and 26.5% of melanoma lesions were increased in a melanocytic nevus. At baseline, 31.4% of melanoma cases had a sentinel lymph node (SLN) biopsy but only one case was positive. Among the atypical Spitz tumour group, three patients had SLN biopsies (13.0%), but none was positive.

Table 1 shows that subjects with atypical Spitz tumour in comparison with subjects with cutaneous melanoma were younger (11.7 versus 15.2 years) $p = 0.0001$, had a lower BMI (19.1 versus 22.3) $p = 0.001$, had no freckles (90.5% versus 60.0%) $p = 0.020$ and had a low number of common nevi (< 25) in the whole body (21.7% versus 64.9%) $p = 0.002$. No differences were found for sex, family history of skin cancer and anatomic site of the lesion between the two groups. Subjects with atypical Spitz tumour tended to have darker skin, eye and hair colour, but the differences were not statistically significant. Only three subjects were exposed to a sun bed and/or lamp. Two of those subjects were in the melanoma group and one in the atypical Spitz tumour ($p = 1.00$).

Table 1 Demographic and clinical characteristics at diagnosis by type of melanocytic lesion

Characteristics	Melanoma (*N* = 51)		Atypical Spitz tumour (*N* = 23)		*p* value[b]
	N.[a]	(%)	*N.*[a]	(%)	
Sex					
Males	27	52.9	11	47.8	
Females	24	47.1	12	52.2	0.803
Age, y					
Mean (SD)	15.2 (4.2)		11.7 (4.8)		0.0001[c]
Age group, y					
< 10.0	4	7.8	9	39.1	
10.0–15.9	20	39.2	10	43.5	
≥ 16.0	27	52.9	4	17.4	0.001
Anatomic site					
Head/neck	8	15.7	2	8.7	
Trunk	20	39.2	5	21.7	
Upper limbs	5	9.8	5	21.7	
Lower limbs	18	35.3	11	47.8	0.251
Family history of skin cancer					
No	47	92.2	20	87.0	
Yes	4	7.8	3	13.0	0.670
Body mass index (kg/m^2)					
Mean (SD)	22.3 (3.6)		19.1 (3.3)		0.001[c]
< 18.5	5	10.9	8	44.4	
18.5–24.9	31	67.4	9	50.0	
≥ 25.0	10	21.7	1	5.6	0.010
Hair colour					
Black/dark brown	22	43.1	11	47.8	
Light brown	20	39.2	11	47.8	
Fair/blond/red	9	17.7	1	4.4	0.332
Eye colour					
Black/dark brown	22	43.1	12	52.2	
Light brown	14	27.5	7	30.4	
Blue/grey/green	15	29.5	4	17.4	0.584
Presence of freckles					
No	27	60.0	19	90.5	
Yes	18	40.0	2	9.5	0.020
Skin photo type[d]					
III–IV	13	25.5	8	34.8	
I–II	38	74.5	15	65.2	0.419
Common nevi (≥ 2 mm)					
0–24	19	38.0	18	78.3	
≥ 25	31	64.9	5	21.7	0.002

[a]Totals may vary because of missing values

[b]Fisher's exact test

[c]Mann-Whitney U test

[d]I: always burns, never tans; II: often burns, tans minimally; III: rarely burns, tans well; IV: never burns, tans profusely

Table 2 shows that the only difference observed between subjects with atypical Spitz tumour and cutaneous melanoma was the history of sunburn episodes. Among the group of atypical Spitz tumour, only 13.0% (versus 49.0%) had a history of sunburns in comparison to cutaneous melanoma cases. In the atypical Spitz tumour group, only 4.3% had a history of two or more sunburn episodes in comparison to 31.4% among the melanoma group ($p = 0.008$). No differences were found for dietary habits, chronic sun exposure and the use of sun protection (the use of hat/or T-shirt or use of sunscreens).

In order to explore if in utero exposure to some environmental factors could affect the type of melanocytic skin tumour, we compared the two groups. No differences were observed regarding maternal exposure to medicine, food supplements, smoking and use of pesticides in the household (indoor/outdoor) between groups (Table 3).

In the multivariate analysis, after controlling for sex and age, a high number of common nevi (≥ 25) (OR 0.28; 95% CI 0.08–0.98, $p = 0.046$) were associated with four times lower risk of atypical Spitz tumour. Older age (≥ 16 years) (OR 0.06; 95% CI 0.01–0.32, $p = 0.001$) was also associated with a lower risk of atypical Spitz tumour. Conversely, both older age and high number of common nevi were associated with an increased risk of melanoma. BMI, the presence of freckles and a history of sunburns were no longer statistically significant after controlling for sex and age (Table 4). It is important to note that age ($p = 0.002$), BMI ($p = 0.021$), presence of freckles ($p = 0.015$), skin photo-type ($p = 0.003$) and history of sunburns ($p = 0.017$) were all associated with number of nevi (Table S1).

Discussion

Given the rarity of both cutaneous melanoma and atypical Spitz tumour in children, it was not known whether children with atypical Spitz tumour differ from children with cutaneous melanoma in terms of etiological factors. In our study, patients diagnosed with atypical Spitz tumour were younger, with a lower BMI, less freckles and a lower number of common nevi and experienced less sunburn episodes in comparison to patients with cutaneous melanoma.

We found no differences between subjects with cutaneous melanoma and subjects with atypical Spitz tumour for hair and eye colour, family history of skin cancer, physical activity, diet, skin photo-type and the use of sun protection measures such as sunscreen use and the use of a hat or t-shirt. No difference was found also for smoking habits of the mother, medicines used during pregnancy and environmental factors such as radiation and pesticide exposure before conception and during pregnancy.

Table 2 Sun exposure and lifestyle before diagnosis by type of melanocytic lesion

Characteristics:	Melanoma (*N* = 51)		Atypical Spitz tumour (*N* = 23)		
	N.[a]	(%)	*N.*[a]	(%)	*p* value[b]
Cumulative hours spent outdoor during the week					
Low (≤ 20)	16	32.7	7	33.3	
Medium (21–34)	16	32.7	9	42.9	
High (≥ 35)	17	34.7	5	23.8	0.612
History of sunburns					
No	26	51.0	20	87.0	
Yes, 1 episode	9	17.6	2	8.7	
Yes, ≥ 2 episodes	16	31.4	1	4.3	0.008
Use of SPF ≥ 15 sunscreens					
Never/rarely	11	21.6	2	8.7	
Often/ever	40	78.4	21	91.3	0.322
Use of hat and/or T-shirt					
Never/rarely	34	66.7	16	69.6	
Often/ever	17	33.3	7	30.4	1.00
Physical activity					
No	6	11.8	4	17.4	
Yes, up to 2 times/wk	24	47.0	13	56.5	
Yes, ≥ 3 times/wk	21	41.2	6	26.1	0.502
Cooked vegetables					
Low (up to 2 times/wk)	22	43.1	11	47.8	
Medium (3–4 times/wk)	14	27.5	7	30.4	
High (≥ 5 times/wk)	15	29.4	5	21.7	0.853
Salad					
Low (up to 2 times/wk)	24	47.1	14	60.9	
High (≥ 3 times/wk)	27	52.9	9	39.1	0.321
Cruciferous vegetables					
Low (less than weekly)	40	78.4	17	73.9	
Medium (1–2 times/wk)	9	17.7	3	13.0	
High (≥ 3 times/wk)	2	3.9	3	13.0	0.395
Leafy green vegetables					
Low (less than weekly)	32	62.8	15	65.2	
Medium (1–2 times/wk)	9	17.6	5	21.7	
High (≥ 3 times/wk)	10	19.6	3	13.0	0.822
Fruits					
Low (up to 4 times/wk)	28	54.9	10	43.5	
Medium (5–7 times/wk)	13	25.5	6	26.1	
High (daily and more)	10	19.6	7	30.4	0.542
Citrus fruits					
Low (up to 2 times/wk)	20	39.2	11	47.8	
Medium (3–4 times/wk)	18	35.3	5	21.7	
High (≥ 5 times/wk)	13	25.5	7	30.4	0.536
Fish					
Low (less than weekly)	26	51.0	8	34.8	
High (weekly and more)	25	49.0	15	65.2	0.218
Fish rich in n-3 fatty acids[c]					
Low (less than weekly)	28	54.9	14	60.9	
High (weekly and more)	23	45.1	9	39.1	0.800

Table 2 (continued)

[a]Totals may vary because of missing values

[b]Fisher's exact test

[c]Sardines, anchovies, tuna and salmon

Table 3 Maternal exposure to drug use, smoking and pesticide exposure by type of melanocytic lesion in their son/daughter

Characteristics	Melanoma (*N* = 51)		Atypical Spitz tumour (*N* = 23)		
	N.[a]	(%)	*N.*[a]	(%)	*p* value[b]
During pregnancy					
Use of drugs					
No	44	89.8	22	95.7	
Yes	5	10.2	1	4.3	0.657
Use of food supplements[c]					
No	30	61.2	15	65.2	
Yes	19	38.8	8	34.8	0.799
Smoking					
No	44	88.0	19	82.6	
Yes	6	12.0	4	17.4	0.715
Between pregnancy and excision					
Smoking status					
Never	31	60.8	12	52.2	
Current	14	27.4	9	39.1	
Quit	6	11.8	2	8.7	0.656
Use of outdoor pesticides					
No	34	66.7	14	60.9	
Yes	17	33.3	9	39.1	0.793
Use of indoor pesticides					
No	10	19.6	4	17.4	
Yes	41	80.4	19	82.6	1.00
Use of repellents during the summer					
No	9	17.7	4	17.4	
Yes	42	82.3	19	82.6	1.00
Use of anti-pediculosis products					
No	16	31.4	8	34.8	
Yes	35	68.6	15	65.2	0.793

[a]Totals may vary because of missing values

[b]Fisher's exact test

[c]For example, folic acid, iron, multivitamins and minerals

The most frequent anatomic site of the atypical Spitz tumour was the lower limbs compatible with other studies, while the trunk was the most frequent site for melanoma [5, 23].

Constitutional risk factors for cutaneous melanoma, which include light skin and hair colour, freckles and propensity to burn (skin photo-type I and II) are genetically determined and unmodifiable. On the other hand,

Table 4 Association between characteristics and type of melanocytic Lesion: uni- and multivariate analysis

	Crude OR[a] (95% CI)	*p* value	adjOR[a,b] (95% CI)	*p* value
Sex				
Males	1		1	
Females	1.23 (0.46–3.29)	0.684	1.36 (0.45–4.10)	0.589
Age group, y				
< 10.0	1		1	
10.0–15.9	0.22 (0.05–0.90)	0.035	0.23 (0.06–0.94)	0.041
≥ 16.0	0.07 (0.01–0.32)	0.001	0.06 (0.01–0.32)	0.001
Body mass index (kg/m^2)				
< 18.5	1		1	
18.5–24.9	0.18 (0.05–0.69)	0.013	0.54 (0.10–2.80)	0.462
≥ 25.0	0.06 (0.01–0.65)	0.020	0.14 (0.01–1.64)	0.117
Presence of freckles				
No	1		1	
Yes	0.16 (0.03–0.76)	0.022	0.21 (0.04–1.18)	0.077
Common nevi (≥ 2 mm)				
0–24	1		1	
≥ 25	0.17 (0.05–0.53)	0.002	0.28 (0.08–0.98)	0.046
History of sunburns				
No	1		1	
Yes, 1 episode	0.29 (0.06–1.49)	0.138	0.63 (0.10–3.82)	0.611
Yes, ≥ 2 episodes	0.08 (0.01–0.67)	0.019	0.18 (0.02–1.69)	0.133

[a]ORs estimate the association of characteristics with atypical Spitz tumour

[b]ORs adjusted for sex and age

sunburns and BMI are modifiable risk factors. In our study, patients with cutaneous melanoma were heavier, had more freckles and had a higher number of common nevi. They also experienced more sunburn episodes in comparison to patients with atypical Spitz tumour. However, in the multivariate analysis only age and number of nevi remained statistically significant. Melanoma patients were older and with more common nevi than patients with atypical Spitz tumour. A study conducted on 1277 school children showed that number of nevi was associated with both high BMI and sun exposure [24]. A recent study confirmed the role of sun exposure on the development of common nevi by demonstrating that improving sun protection habits can decrease the number of common nevi in children [25] and thus the risk of melanoma. The role of obesity on melanoma is controversial [26], but it has been suggested that it impairs the capacity of DNA repair in melanocytes [27].

To our knowledge, this study is the first of its kind that obtained detailed information on individual and environmental factors in children with melanoma or atypical Spitz tumour. Melanoma is the deadliest skin cancer, and thus knowledge about risk factors is important for prevention. Moreover, knowledge about differences between melanoma and atypical Spitz tumour may help in the early diagnosis.

The limitations of the study include the impossibility of conducting a separate analysis for this particular age group due to the low number of persons below the age of 10 years. Another limitation of the study is the recall bias that is an inevitable problem of observational studies. However, using incident cases decreases the possibility of misclassification of the exposure.

From the findings of this study, it is suggested that the only difference between cutaneous melanoma and atypical Spitz tumour in terms of individual and environmental risk factors is the number of nevi. Knowledge of risk factors for cutaneous melanoma in children and the differences between cutaneous melanoma and atypical Spitz tumour may help family doctors in referring patients to dermatological clinics and thus improving early diagnosis.

A multicentre study with a larger sample size from different geographic regions is warranted to confirm our findings.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s00431-021-04204-x.

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Authors' contributions Fortes Cristina has conceived, designed and supervised the conduct of the study and has participated in the data analysis and interpretation. She has written the manuscript and collected comments from co-authors. Mastroeni Simona has managed and analysed data applying the appropriate statistical methods and has critically revised the manuscript; Capuano Maria collected the data, provided input on specific issues and has critically revised the manuscript; Ricozzi Ilaria collected the data, provided input on specific issues and has critically revised the manuscript; Bono Riccardo collected the data, provided input on specific issues and has critically revised the manuscript; Ricci Francesco collected the data, provided input on specific issues and has critically revised the manuscript; Pagnanelli Gianluca collected the data, provided input on specific issues and has critically revised the manuscript; Nudo Maurizio collected and supervised data collection, provided input on specific issues and has critically revised the manuscript.

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Declarations

Ethics approval This study was performed in line with principles of the Declaration of Helsinki. Approval was granted by the Ethical Committee (no. 425 CE/2014) of the Istituto Dermopatico Dell'Immacolata Concezione (IDI-IRCCS).

Consent to participate Written informed consent was obtained from parents and individuals participating in the study.

Conflict of interest The authors declare no competing interests.

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